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SPRINGER-VERLAG / BERLIN · GÖTTINGEN · HEIDELBERG

(Postverlagsort Berlin · 19. 12. 1961)

Die Forschung über die Wirkungen und Wirkungsweisen psychotroper Substanzen hat in den letzten Jahren einen unerhörten Aufschwung genommen. Was vordem nur ein erwünschtes Ziel war, ist zu einer neuen Wissenschaft geworden: Psychopharmakologie. Da eine fruchtbare Analyse und Synthese ihrer Probleme nur durch Zusammenarbeit aller Grundfächer (Pharmakologie, Neurochemie, Neurophysiologie, Neurologie, Psychologie und Psychiatrie) möglich wird, ist die Psychopharmakologie eine verbindende, integrierende Forschungsdisziplin. Die ständig anwachsende Literatur dieses komplexen Arbeitsgebietes ist jedoch bisher zwangsläufig über zahlreiche Zeitschriften verstreut, da es bis heute kein Spezialorgan gab, das sich ausschließlich der Psychopharmakologie widmet. Diesem dringenden Bedürfnis zu begegnen, hat sich eine Gruppe von Vertretern der verschiedenen Arbeitsrichtungen der Psychopharmakologie entschlossen, eine neue Zeitschrift „Psychopharmacologia" zu gründen. In ihr sollen die bedeutenden Fortschritte dieses Arbeitsgebietes durch Veröffentlichung experimenteller und klinischer Originalarbeiten, Übersichten der neuesten Literatur sowie kurzer Originalmitteilungen zusammengefaßt werden.

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Recent years have witnessed an unprecedented advance in research on the action and effects of psychotropic drugs, and what, formerly, was just a distant goal, has now evolved into a new branch of science: psychopharmacology. As, however, any fruitful analysis and synthesis of its problems can only be attained with the aid of the complete scale of basic sciences (pharmacology, neurochemistry, neurophysiology, neurology, psychology and psychiatry), psychopharmacology constitutes an integrating discipline of research. Owing to the lack of an organ devoted especially to psychopharmacology, the constantly increasing literature pertaining to this complex field of activity has hitherto of necessity been scattered among various periodicals. In order to overcome this drawback, a group of representatives of the various psychopharmacologic sections have engaged in editing a journal, "Psychopharmacologia", in which the publication of original experimental and clinical papers, reviews of recent literature and short original notices will provide a comprehensive survey of the important progress which is being actually achieved in this field of science.

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Ces dernières années ont vu un développement sans précédent dans la recherche des effets et du mode d'action des substances psychotropes sur le «Comportement» et ont fait naître une nouvelle science: la Psychopharmacologie. Comme ces problèmes ne peuvent être résolus que par la collaboration des disciplines de base telles que la pharmacologie, la neurochimie, la neurophysiologie, la psychologie et la psychiatrie, la psychopharmacologie est devenue un champ de recherche de première importance. Cependant la littérature toujours croissante en ce domaine de recherche est forcément disséminée dans de nombreux périodiques, puisqu'il n'existe pas encore de journal exclusivement consacré à la psychopharmacologie. Pour répondre à ce pressant besoin un groupe de représentants des diverses disciplines de la psychopharmacologie s'est mis en devoir de rédiger un nouveau journal dans lequel seraient rassemblés les progrès importants de ce domaine, par la publication d'ouvrages originaux expérimentaux et cliniques, ainsi que des rapports sur des questions actuelles.

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# Psychopharmacologia

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Psychopharmacologia 2, 381—407 (1961)

*Original Investigations · Originalarbeiten · Travaux originaux*

From the University Psychiatric Clinic, Burghölzli, Zürich
(Director: Prof. Dr. med. M. BLEULER)

# A Clinical Analysis of the Effects of Tofranil in Depression

## Longitudinal and follow-up studies. Treatment of blood-relations

By

J. ANGST

With 3 Figures in the Text

*(Received July 13, 1961)*

### A. Purpose of the study

The exact mode of action of most of the psychotropic drugs is as yet largely unknown, despite intensive biochemical research. Thus the basis for the antidepressant effect of imipramine (Tofranil) has not yet been elucidated, although more than 3 years have passed since its introduction. Studies are therefore still centred on the clinical action of the drug. After the successful results of Tofranil treatment reported by KUHN (1957) had been confirmed in numerous publications, interest was directed towards particular problems such as combination-therapy or comparison with other methods of antidepressant treatment.

The present study aims at furnishing further clinical results. It comprises a case-material of 200 patients treated with Tofranil, 137 of whom were suffering from endogenous depression. An attempt is made to establish whether apart from nosological aspects and the psychopathological condition, there exist other factors which influence the results of treatment, e.g. psychoses in the family, constitution, sex, age, premorbid personality, age of onset of illness, duration of disease, duration of separate phases, course of psychosis etc. Moreover, by means of longitudinal studies (comparison of the separate phases), the results of treatment with Tofranil are compared with those of other, earlier and later, therapeutic procedures. Finally the follow-up results and the question of a similarity in action of Tofranil among blood-relations are considered.

### B. Methods

For $1^1/_2$ years all patients admitted to our hospital with endogenous depression and depressive-schizophrenic mixed psychoses were treated with Tofranil.

The patients were examined by the author in several clinical respects, whereas treatment was conducted by other members of the staff in the majority of cases. In every case a detailed analysis of the psychopathological condition was performed, taking into account the sub-

jective and objective symptoms. The separate symptoms were statistically evaluated; if necessary the Rorschach-test and Hamburg-Wechsler-intelligence test were employed. The behaviour in occupational therapy and in the wards was included in the assessment. Objective insight into the life history and premorbid personality was gained from enquiries, previous case histories and documents. The results of the investigations were statistically recorded on punched cards.

The medical history of the patient and of his family were recapitulated and elaborated. Especial weight was laid upon finding psychotic relatives with a view to treating these with Tofranil. In all cases relatives were repeatedly questioned either personally, by telephone or by letter. Care was taken not to centre treatment on the doctor carrying out the investigations, so as not to place patients treated with Tofranil in a special position within the routine of the hospital. This procedure offers the further advantage that several doctors are in a position to assess the results of treatment.

### C. Case-material and results of treatment

150 were in-patients, 50 out-patients. *105 in-patients with endogenous depression form the nucleus of our investigations.* An exact analysis of the out-patient results was not possible, as the imponderables of treatment under these conditions are too great to permit conclusive answers to our questions.

Our investigations are concerned primarily with endogenous depression because this is the chief indication for Tofranil and because it presents a relatively homogenous material for experimental purposes. In some cases diagnostic classification is difficult because, as BLEULER points out, manic-depressive psychosis (MDP) shows gradual transitions to other clinical entities (involutional psychoses, involutional depression, climacteric depression). In the present investigation we followed STENSTEDT in classifying endogenous depressions occurring after the menopause in women and after the 45th year of age in men, and showing no hypomanic phases, among the involutional depressions. As soon as the object of the inquiry could be served by so doing, depressions of the involutional period which showed a recurrent, phasic character were sorted out from involutional depressions and classified among the MDP.

The *results of treatment* are divided from the clinical point of view into 5 groups:

| | |
|---|---|
| Depressive condition aggravated under Tofranil | — |
| Depressive condition unchanged | 0 |
| Improvement insufficient | + |
| Improvement satisfactory; in general, place in society resumed and discharge from hospital | ++ |
| Freedom from symptoms; full remission | +++ |

The first three groups are considered as failures, the last two groups as successes of treatment. It should be noted that, as compared with other studies, the criteria for clinical success are fairly strict. If a patient could not be discharged from hospital under treatment with Tofranil, treatment was usually judged to be insufficiently successful (+), and therefore on the whole a failure. Although this is a somewhat rough evaluation (e.g. no rating scale was employed), it avoids autosuggestive overestimation of minute details observed under treatment.

Table 1 illustrates both the diagnostic classification of our case-material and the results of treatment with Tofranil. It clearly confirms the favourable experiences gained to date by numerous authors in the treatment of endogenous depression with Tofranil. *66% of our patients admitted with a diagnosis of endogenous depression responded well or very well to Tofranil.* In particular it seems, noteworthy that the response of involutional depressions to Tofranil is at least equal to that of endogenous depressions.

Table 1. *Diagnoses and results of treatment with Tofranil*

| Diagnosis | Number of cases | Results of treatment: Success +++ | Success ++ | Failure + | Failure 0 | Failure — | Successes in % |
|---|---|---|---|---|---|---|---|
| A. In-patients . . . . . Total | 150 | | | | | | |
| *Endogenous depression* . . . . . | 105 | 17 | 52 | 6 | 24 | 6 | 65.7 |
| Manic-depressive psychosis: 41 . . | | 7 | 19 | 3 | 10 | 2 | 63.4 |
| Involutional depression: 43 . . . | | 7 | 23 | 3 | 10 | — | 69.6 |
| Recurring in phases: (17) . . . . | | (3) | (7) | (1) | (6) | — | 58.8 |
| Climacteric depression: 6 . . . . | | 1 | 3 | — | 1 | 1 | |
| Uncertain as regards sub-group: 15 | | 2 | 7 | — | 3 | 3 | |
| *Depressive-schizophrenic mixed psychosis* . . . . . | 24 | 2 | 15 | 3 | 4 | — | 70.8 |
| Depression associated with arterio-sclerosis . . . . . | 2 | 1 | 1 | — | — | — | |
| Schizophrenic depression . . . . . | 7 | — | 4 | — | 3 | — | |
| Neurotic depression . . . . . | 2 | — | 1 | 1 | — | — | |
| Reactive depression . . . . . | 7 | 2 | 1 | 3 | 1 | — | |
| Postencephalitic depression . . . . | 1 | — | 1 | — | — | — | |
| Epileptic depression . . . . . | 2 | — | 1 | 1 | — | — | |
| B. Out-patients . . . . . Total | 50 | | | | | | |
| *Endogenous depression* . . . . . | 32 | 12 | 13 | 4 | 3 | — | 78.0 |
| Manic-depressive psychosis: 17 . . | | 6 | 6 | 3 | 2 | — | |
| Involutional depression: 11 . . . | | 3 | 6 | 1 | 1 | — | |
| Climacteric depression: 4 . . . . | | 3 | 1 | — | — | — | |
| *Depressive-schizophrenic mixed psychosis* . . . . . | 4 | 1 | — | — | 3 | — | |
| Reactive depression . . . . . | 7 | 3 | 2 | — | 2 | — | |
| Neurotic depression . . . . . | 6 | 1 | 2 | 2 | 1 | — | |
| Senile depression . . . . . | 1 | — | — | — | 1 | — | |
| Total of patients treated . . . . . | 200 | | | | | | |

In the evaluation of the results for the special purposes of this study, only in-patients suffering from endogenous depressions or mixed psychoses were taken into account. The remaining case-material was utilized only for the investigations on the side-effects.

**D. Relationship between the results of treatment and group characteristics not primarily related to the disease**

**1. Age.** Reports found in the literature on the influence of age on the results of treatment are contradictory. FLEGEL, FREYHAN (1960) and HIFT et al. consider that the therapeutic response becomes less with increasing age; according to KUHN the influence of age is uncertain. Other detailed investigations [BRUCE et al., CLEVELAND et al., KRAKOWSKI, LESSE, MEUSERT, SCHMITT (1959)] speak against an influence of age. KRAKOWSKI supports his conclusions with exact figures. According to our own investigations, age has no statistically significant influence on the results of treatment. Below, the question is examined whether age exerts an indirect, unfavourable influence on the prognosis by means of its pathoplastic effect, e.g. by increasing the incidence of agitated depressions, which respond badly to Tofranil.

**2. Sex.** Of 78 women with endogenous depression 62.3%, and of 27 men 74.7%, responded well to Tofranil. This difference is not statistically significant.

Originally, in a smaller number of cases (70), the difference in results between men and women was more pronounced, wrongly suggesting that men show a far more favourable response. This clearly shows how misleading such summary observations can be. Later on it was established that the response to Tofranil is distinctly dependent on the number of phases. In our case-material the incidence of first attacks, which respond particularly well, was, by chance, higher among the men.

On principle it is questionable whether the results of treatment should be grouped according to sex, and it is therefore not surprising that the observations in the literature are contradictory. According to FREYHAN (1960), KUHN and MACLEAN et al., women show a better response to Tofranil than men, whereas KRAKOWSKI, LESSE, SCHNEIDER et al., and STOLLER established no sex-dependence.

Table 2. *Constitution and effect of Tofranil*

| Constitution | Results | |
|---|---|---|
| | Success | Failure |
| Pyknic . . . . . | 31 | 15 |
| Leptosomatic . . | 21 | 12 |
| Athletic . . . . . | 10 | 6 |
| Uncertain . . . . | 6 | 4 |

**3. Constitution.** Constitution has no influence on the results of treatment; in particular pyknic patients show no better response. These observations confirm those of TELLEZ et al.

**4. Premorbid personality.** The premorbid personality was studied in the greatest possible detail. Syntonic characteristics did not preponderate in our case material; 48 out of 105 patients were schizothymic, and only 13 cyclothymic. The high incidence of premorbid conscientious-pedantic personality-structures is remarkable (29 out of 105). 7 patients were oligophrenic.

*The premorbid personality-structure was found to have no influence whatsoever on the results of treatment of endogenous depression.* TELLEZ et al. reach the same conclusions. The premorbid personality does not affect the efficacy of Tofranil, whether the patients are cheerful, tend to take everything to heart or are syntonic. Moreover, as CLEVELAND et al. also state, intelligence seems to be of no importance.

**5. Heredity and endogenous psychoses.** The familial incidence of endogenous psychosis was studied among the close relations, i.e. parents, siblings and children.

Table 3. *Endogenous psychoses in the family and results of treatment*

| Endogenous psychoses in the family | Patients | Results of treatment | | | | |
|---|---|---|---|---|---|---|
| | | +++ | ++ | + | 0 | — |
| None . . . . . | 56 | 7 | 31 | 4 | 11 | 3 |
| Endogenous depression . | 39 | 7 | 16 | 2 | 12 | 2 |
| Schizophrenia . . . . . | 11 | 3 | 5 | — | 2 | 1 |

DELAY et al. (1959c) and TSCHUDIN are of the opinion that patients with the same form of endogenous psychosis in the family respond better to treatment than the other groups. The figures cited by DELAY do not, however, appear to be statistically significant, and TSCHUDIN does not give detailed figures. Our own results furnish no certain indications for assuming a relationship between the response to Tofranil and the presence of endogenous psychosis in the family. In our compilement, patients without psychosis in the family appear to respond somewhat better to treatment with Tofranil. The difference is, however, not sufficiently significant to permit definite conclusions.

**6. Summary.** On the basis of the examination of 105 cases of endogenous depression, it could be established that age, sex, constitution, premorbid personality and probably also the occurrence of endogenous psychosis in the family do not influence the therapeutic effect of Tofranil.

## E. Relationship between the results of treatment and factors primarily related to the disease

**1. Age at first attack.** In conformity with SCHMITT (1959) we established that the age at the time of the first attack had no influence on the

results of treatment. If the first attack occurred in the first 50 years of life, we achieved 64.4% successes, in the second half of life 68.3%.

**2. Number of phases.** SCHMITT (1959) reports contradictory results on the influence of the number of phases. FREYHAN (1960), PAKESCH et al. and SELBACH are of the opinion that patients suffering from a first attack respond better to treatment than patients who have had previous attacks.

Table 4. *Number of phases and results of treatment*

| Number of phases | Number of patients | +++ | ++ | + | 0 | — | Q Success-rate |
|---|---|---|---|---|---|---|---|
| 1st phase . | 36 | 8 | 20 | 2 | 4 | 2 | 28: 8 |
| 2nd phase . | 25 | 2 | 14 | — | 8 | 1 | 16: 9 |
| Later phase | 40 | 6 | 16 | 4 | 12 | 2 | 22:18 |

Already in the second phase a certain decrease in the rate of successes is evident. The difference is not statistically significant ($P = 0.25$*). Among patients with later phases, only 55% responded to Tofranil. The difference in the results of treatment from those achieved in first phases is statistically significant ($P = 0.04$).

*It is thus established that the results of treatment with Tofranil are less favourable as the number of phases increases.* This conforms with the clinical observation that, not only in electric shock therapy, but also in treatment with Tofranil, resistance to therapy may appear in later phases. The question arises, whether the fact that the duration of the phases is prolonged with the increase in their number is related to these findings (POLLOCK). SELBACH explains the development of resistance to therapy with a decline in the activity of autonomic control mechanisms.

**3. Course.** The various courses of the illness in our patients with endogenous depression were grouped as follows:

Recurrent depressive course,

Cyclic manic-depressive course,

Simple chronic depressive course.

Table 5. *Course and results of treatment*

| Course | Number of patients | +++ | ++ | + | 0 | — | Q |
|---|---|---|---|---|---|---|---|
| Recurrent-depressive . . | 55 | 8 | 27 | 2 | 16 | 2 | 35:20 |
| Manic-depressive . . . . | 7 | 2 | 2 | 1 | 2 | — | 4:3 |
| Chronic-depressive . . . | 16 | 1 | 7 | 2 | 4 | 2 | 8:8 |

The majority of the cases belonged to the group of recurrent depression.

* Calculated with the aid of the chi²-distribution.

As was to be expected [cf. SCHMITT (1959)], the best results were achieved in recurrent depression. As also stated by KIELHOLZ et al. the response in cyclic forms was slightly worse, whereas this was found by DELAY et al. to be somewhat better. It is noteworthy that, even in chronic depression, 50% of the patients still showed a relatively good response.

**4. How long the phase had already lasted when treatment was begun.** Presented graphically (Fig. 1), the chances for successful treatment within the first 12 months of a depressive phase take a practically horizontal course, and only decline after 1 year. The reduction in the chances of success was statistically verified in 101 cases analysed ($P = 0.015$).

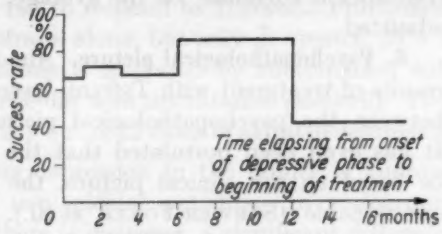


Fig. 1. Success-rates achieved with Tofranil in relation to the point in the depressive phase at which treatment was begun

It seems of significance that the chances of success are equal in the first and second half-years of a phase. If the spontaneous duration of a phase were assumed to be 9—12 months, and if the remissions under Tofranil were ascribed to the spontaneous course alone, the curve would have to take a different course. Patients in the first half-year of a phase would then most probably show a more unfavourable response to Tofranil than the majority of those commencing treatment in the second half-year. Our results therefore suggest that the positive effect of Tofranil does not merely coincide with spontaneous remission; they do not, however, establish any definite proof.

The results of treatment achieved in *first attacks in relation to the duration of the phase* are particularly impressive. Among 22 patients who had been ill for less than 1 year when treatment was begun, 20 remissions were observed under Tofranil. As a contrast, first attacks in patients who had suffered from depression for more than 1 year were successfully treated in only 8 out of 13 cases.

**5. How long the patient had been in hospital when treatment was begun.** On the average the prognosis in recently hospitalized patients is naturally better. As can be seen from the Table 6, treatment was therefore more successful in these cases.

Therapeutic response falls away steeply the longer the patient has been in hospital. A comparison with the observations in section 4 above shows how important it is to distinguish how long the patient has been *in hospital* from how long his *depressive phase* has lasted. Patients who have been in hospital for a considerable length of time have usually failed to respond to other therapeutic procedures; the indidence of

Table 6. *Effect of Tofranil in relation to how long the patient had been in hospital when treatment was begun*

| Period already in hospital | Number of patients | +++ | ++ | + | 0 | — | Q |
|---|---|---|---|---|---|---|---|
| 1— 4 days . . . . . | 63 | 12 | 33 | 2 | 14 | 2 | 45:18 |
| 5—14 days . . . . . | 7 | — | 5 | — | 1 | 1 | 5:2 |
| 15—30 days . . . . . | 4 | 1 | 1 | 1 | — | 1 | 2:2 |
| 31—90 days . . . . . | 8 | 1 | 2 | 1 | 4 | — | 3:5 |
| 4— 6 months . . . | 7 | — | 2 | 1 | 4 | — | 2:5 |
| 7 months or more . . | 2 | 1 | — | 1 | — | 1 | 1:1 |

resistance is therefore, on the average, higher than in patients recently admitted.

**6. Psychopathological picture.** Almost all the clinical reports on the results of treatment with Tofranil have tried to establish a relationship between the psychopathological picture and the therapeutic results. It has even been postulated that the indications for Tofranil should be based on the clinical picture, the part played by nosology being questionable (SARWER-FONER et al.). Here the concept of "target symptoms" (FREYHAN 1959) has become a leading principle. It has been established that the primarily inhibited forms of depression respond best to Tofranil (AYD, ANGYAL, COIRAULT et al., FAZIO et al., HEINZE, HIFT et al., KUHN, TRUEB). Stuporous conditions are less responsive (HOFF); in conditions of stupour HIFT et al. found Tofranil to be ineffective, whereas MIVELAZ observed a relatively good response.

Opinions differ as regards the influence of Tofranil on anxiety. FAZIO et al., FLEGEL, SCHNEIDER et al. established good, TRUEB and HIFT et al. unsatisfactory, and AZIMA, SLOANE et al. no response whatsoever. On the whole there is agreement that depressive delusional symptoms (HIPPIUS 1959), hypochondriacal ideas (TRUEB) and, above all, agitation (HIFT et al., HIPPIUS, KUNZ, MIVELAZ) prejudice the results of treatment. KRAKOWSKI, however, who should be mentioned on account of his thorough investigations, declares that agitation does not influence the efficacy of Tofranil.

We have also grouped our case-material according to psychopathological aspects. Inhibited forms of endogenous depression respond by far the best to Tofranil (76%); but even among the classic cases impressive failures are encountered, as was already pointed out by FREYHAN in 1959. Patients with vital depression (K. SCHNEIDER), who experience sadness as a localized bodily sensation, and patients with primary feelings of guilt (WEITBRECHT), respond relatively well (64% successes). Out of 6 cases with depressive stupor 3 failed to respond. Anxiety is very common in our case-material. 73 out of 105 patients complained of feelings of anxiety. Among these, $^2/_3$ responded favourably

to Tofranil. Anxiety without agitation does therefore not seem to prejudice the chances for successful treatment.

Age does not directly influence the responsivity to Tofranil. Indirectly, however, the pathoplastic influences of increasing age reduce the success-rate achieved with Tofranil. Above the age of 50 there is a distinct increase in agitation, hypochondriacal ideas, paranoid symptoms and delusions of poverty. Paranoid symptoms in the depressive picture do not diminish the success of treatment. Hypochondriacal delusions, ideas of poverty and, above all, agitation have, however, a very unfavourable influence. We cannot agree with MEYER that agitated, forms of depression completely fail to respond to Tofranil. Pronounced agitation may subside under Tofranil alone, but only in approx. 25% of the cases. The incidence of success is increased by combination with phenothiazine derivatives, in particular with thioridazine (Melleril). Thus successful results were achieved in 9 out of 22 cases of agitated depression.

The incidence of endogenous depression in the family is approximately equal in suicidal and non-suicidal patients. In endogenous depressions with suicidal ideas there is, however, a significant difference if the following two groups are compared: in the family of patients who attempted suicide or uttered ideas of suicide the incidence of suicide is approximately twice as high (39.2%) as in the family of non-suicidal patients (23.2%). Tendency to suicide has no influence on the effect of Tofranil. We do not agree with the frequently encountered opinion (MOORE) that electric shock treatment should be applied in cases of overt risk of suicide.

**7. Reactive features.** Simplifying, we may distinguish in endogenous depression between *reactive mechanisms* which have influenced the development of the patient's illness over a prolonged period (e.g. tension between husband and wife), and *precipitating reactive factors*. In the latter we include sudden events or conflicts which closely precede the onset of psychosis, e.g. accidents, death of a relative, retirement from work, change of environment. Sudden precipitating situations in endogenous depression were present in 17 patients, i.e. in 16%; 16 of these patients were above 45 years of age! Chronic reactive mechanisms were established in 14 cases.

Precipitating factors in the separate phases of manic-depressive psychosis do not occur regularly. Longitudinal studies show that one or several phases may appear to have been precipitated by exogenous causes; other phases in the same patient may be of purely endogenous character. Moreover, in the same patient, sudden emotional stresses occurring in an interval, e.g. death of the husband, do not necessarily unleash a further phase.

According to our observations *precipitating factors have no influence on the results of treatment.* They have neither a favourable nor an unfavourable influence on the course of the phase under Tofranil. The incidence of success in endogenous psychoses with reactive features is 74%, in the other cases 60%. The difference is not statistically significant.

According to LANGE the contents of depressions precipitated by psychological mechanisms are not determined by the precipitating event. Our case-histories confirm this observation. PAULEIKHOFF rightly points out that precipitating factors are found chiefly in patients whose interests are fixed and restricted and who are often limited and narrow-minded. From the age-distribution of our case-material it seems probable that the characteristics described by PAULEIKHOFF must be attributed to the pathoplastic influence of age. *Increasing age heightens the readiness to reactive precipitation of endogenous depressive phases.*

8. **Organic features.** 13 among the 105 cases of endogenous depression were suffering simultaneously from a mild amnestic syndrome. From the Table 7 it can be seen that only 6 out of 13 patients responded

Table 7. *Age-distribution, organic features and results of treatment*

| Age | Number of cases | +++ | ++ | + | 0 | — |
|---|---|---|---|---|---|---|
| 20—29 | 1 | | 1 | | | |
| 30—39 | 1 | | | | | 1 |
| 40—49 | 1 | | 1 | | | |
| 50—59 | 2 | | 1 | 1 | | |
| 60—69 | 6 | 1 | 1 | | 4 | |
| 70—79 | 2 | | 1 | | 1 | |

favourably to treatment. The case-material is too meagre to be statistically conclusive. As opposed to DELAY et al. and TSCHUDIN, and in agreement with DE LA CRUZ, HARRER et al., HEINZE, KUHN, KUNZ, KEUP and STRAKER et al., we nevertheless consider that the results of treatment are prejudiced if organic components are involved in the depressive condition.

### F. Mode of administration and dosage

Whenever possible treatment was initiated with injections of Tofranil, administered for a period of 8—14 days, and followed by a sudden change to the same dose of tablets; detrimental effects were never observed. In conformity with BADER and COLIN, and contrary to the recommended procedure, we did not initiate treatment gradually. On the first day of treatment we usually administered 4 intramuscular injections of Tofranil 25 mg each, and already on the second day 4 of 50 mg each. Naturally lower individual doses were necessary in many cases. As a rule gradually

increasing dosage is not indicated (COLIN, FREYHAN 1960, SCHMITT 1959). If the depressive condition did not improve within 2 weeks, treatment was considered a failure and withdrawn. We did not continue therapy in the absence of success, as remissions occurring at a later date cannot be ascribed with certainty to treatment, the therapeutic effect no longer being clearly distinguishable from spontaneous remissions.

AZIMA and HIFT et al. are of the opinion that parenteral administration is not superior to oral treatment; according to FAZIO et al. the dosage also has no direct influence. Our own results permit no decisive conclusions as regards either statement. Among 66 patients treated parenterally 69% successes were achieved; among 39 patients treated by mouth 59% showed a favourable response. The ratio remains the same if equal doses are taken as a basis for the evaluation. The difference of 10% is unclear and statistically insignificant. Individual observations point in the same direction (BADER): several of our patients responded only to injections of Tofranil, even if the oral dosage of Tofranil was greatly increased. A change to tablets was followed by relapse, which could be immediately overcome by re-establishing parenteral treatment.

The same mode of administration, but with different dosages, also yielded a slight difference in the results of treatment: dosages above 150 mg daily gave a slightly higher success-rate than smaller quantities.

The *duration of treatment* is determined by the response. Among our patients treated for 1—3 weeks with Tofranil, 24 responded well and 16 poorly. If treatment was carried out for 4—8 weeks the success-rate was higher (41 successes, 9 failures). This difference is explained by the fact that side-effects necessitating withdrawal of treatment are usually observed within the first 8—14 days. Treatment lasting for 4—8 weeks is generally sufficient to permit discharge from hospital.

In patients treated successfully with Tofranil the average *stay in hospital* after commencement of treatment of endogenous depression is 43 days. SCHMITT (1959) calculated 28—32 days. Studying the course in separate cases FREYHAN reached the conclusion that the stay in hospital is not significantly changed through Tofranil therapy. It is very difficult to establish whether Tofranil is able to shorten the time spent in hospital. We restricted ourselves to comparative investigations within our case-material of endogenous depressions. In first admissions not receiving Tofranil (57 cases) the stay in hospital is 80 days. Under treatment with Tofranil (38 cases) the corresponding figure is 50 days. In the second phase of the illness the average stay was 107 days for patients without Tofranil therapy (38 cases), and 88 days for treated patients (21 cases). In later phases the stay under Tofranil is also 90 days (44 cases). *It is thus possible that Tofranil is able to shorten the stay in*

*hospital*. In our case-material the reduction is 30 days (37%) for first admissions and 19 days (19%) for later phases. This curtailment cannot be ascribed with certainty to Tofranil, since all the factors involved cannot be taken into account. Thus other recent developments in hospital treatment and the scarcity of beds may also contribute to an earlier discharge.

As a rule withdrawal of Tofranil therapy was not allowed to coincide with discharge from hospital. Either treatment was discontinued approximately 2 weeks before discharge, or out-patient therapy was carried out. Particularly in involutional depressions, treatment at home was often continued for several months or more. This measure should, however, only be observed as long as depressive symptoms are present or if they should reappear when treatment is interrupted. There would be no sense in prescribing "prophylactic" therapy against further attacks.

### G. Treatment of mixed psychoses with Tofranil

24 cases suffering from depressive-schizophrenic mixed psychoses were treated with Tofranil. We shall not discuss the problems arising in the diagnostic differentiation of these pictures. In general they gave the impression of endogenous depression, to which were added occasional schizophrenic symptoms during the attack, or in which schizophrenic personality disorders (resulting from previous schizophrenic phases) were present during the intervals. It can be seen from the Table 8 that the results of treatment tend to be favourable:

Table 8. *Mixed psychoses treated with Tofranil*

| | Number | +++ | ++ | + | 0 | — | Success-rate |
|---|---|---|---|---|---|---|---|
| Women . . | 18 | 2 | 12 | 1 | 3 | — | 14:4 |
| Men . . . | 6 | — | 3 | 2 | 1 | — | 3:3 |
| Total | 24 | 2 | 15 | 3 | 4 | — | 17:7 |

Although complete freedom from symptoms is practically never achieved, discharge from hospital was possible in 17 out of 24 cases. Most likely these successful results may be attributed to the fact that the depressive states were of the inhibited form, and that the illness took a phasic course. So far only two cases of mixed psychosis were of the chronic type, and both of these failed to respond to Tofranil. It would, however, be unjust to ascribe the remissions observed under Tofranil therapy to the spontaneous course. The impressive and rapid improvements and the prompt aggravation upon withdrawal of treatment clearly speak against such an interpretation.

In mixed psychoses accompanied by paranoid symptoms or slight agitation, combination with phenothiazine derivatives is advisable. DELAY also pointed out the value of this combination.

The good results achieved in depressive-schizophrenic mixed psychoses show that the schematic conception that, within a certain group of cases, the results are the better the larger the so-called "nucleus" of vitally depressed, inhibited pictures, does not quite correspond to the actual situation. Provided that the indications are adhered to, depressive conditions accompanied by schizophrenic symptoms may show an equally favourable response to Tofranil. The schizophrenic symptoms themselves are usually not improved. Naturally schizophrenia itself is not included in the field of indication for Tofranil. Exacerbation or "unmasking" of paranoid symptoms may be observed under Tofranil; catatonic manifestations (also stupour), in which inhibition predominates, respond little or not at all to Tofranil. Nevertheless, inhibited-depressed forms of schizophrenia and mixed psychoses often show a surprising "lightening of the mood" under Tofranil.

### H. Side-effects

The reports in the literature on the incidence and severity of side-effects are extremely varied. This must be ascribed, in part, to differences in the thoroughness of observation and in the dosage. According to BARUK more side-effects are observed under parenteral treatment. Autonomic disturbances are more frequent in women than in men (KUHN and LEHNER). Several authors state that age has an uncertain (LEHNER) or aggravating effect (DELAY et al., HIFT et al., LEHMANN et al.). Tremor is supposed to be more frequent in older patients (ENGLISH).

In our case-material side-effects were observed in 108 out of 150 patients, i.e. in 72%. In descending order of frequency they were as follows:

Table 9. *Side-effects*

| | Number of patients | % | | Number of patients | % |
|---|---|---|---|---|---|
| Dryness of mouth | 76 | 50 | Constipation | 5 | 4 |
| Sweating | 34 | 24 | Collapse | 4 | 3 |
| Disturbances in accommodation | 17 | 12 | Severe somnolence | 4 | 3 |
| Giddiness | 17 | 12 | Paraesthesiae | 3 | 2 |
| Tremor (fine) | 16 | 11 | Allergic exanthema | 3 | 2 |
| Thirst | 11 | 7 | Pruritus | 2 | 1.3 |
| Tiredness | 11 | 7 | Disturbances in micturition | 3 | 2 |
| Disturbances in sense of taste | 9 | 6 | Parkinsonism | 3 | 2 |
| Palpitations | 9 | 6 | Infiltrations caused by the injection | 6 | 4 |
| Nausea | 5 | 4 | | | |

We found no relationship between the incidence of side-effects and sex; this is also true if the separate side-effects are evaluated. Older patients appear to have a greater tendency to side-effects, and therapy should therefore proceed with extreme caution. Combination with phenothiazine derivatives leads to a significant enhancement of side-effects.

Atropine-like effects are the most frequent. They are manifest in the form of dryness of the mouth and pharynx, deep voice, possibly slight hoarseness, conjunctival irritation, etc. Disturbances in the sense of taste (PICHLER) are more frequent than might be expected from the literature, and may become very unpleasant.

Psychotic side-effects have frequently been reported. We occasionally observed dysphoria or agitation, 1 case of manic excitation, and 3 cases of psychoses of the nature of an "acute exogenous reaction" (BONHOEFFER). These complications appear to occur in patients with an individual predisposition. Thus in 1 case acute psychotic attacks recurred at intervals of a few weeks under chlorpromazine, thioridazine and finally under Tofranil. These complications once more confirm the relationship between these substances. Here we would also mention the sedative effect of Tofranil; tiredness or somnolence was manifested in 10% of the cases. The tendency to suicide was not enhanced under Tofranil.

In 8 cases (6%) treatment had to be withdrawn on account of side-effects. These were: disturbances in sense of taste, coarse tremor, Parkinsonism, exanthema, paraesthesiae, agitation and an acute psychotic attack.

Endocrine side-effects are infrequent. In one case a pronounced enlargement of the breasts and galactorrhoea of several weeks' duration could be ascribed with certainty to Tofranil. In a young girl slight hirsutism was observed. Despite their rarity these side-effects are of great interest, as they once more show that Tofranil and the neuroplegic drugs are closely related.

We attached great value to elucidating the question whether a relationship exists between the manifestation of side-effects and the therapeutic success. A certain evaluation was possible in 134 of our patients, 116 of whom (86%) showed side-effects. The success-rate in patients with side-effects is 82:34 (70%), that in patients without side-effects 9:9 (50%). Conclusions can hardly be drawn from these figures. The prognosis appears particularly favourable in the presence of giddiness, sweating and thirst.

In 5 out of 150 cases the depressive attack was followed by a hypomanic phase. It has as yet not been established whether treatment can be held responsible.

## J. Comparison of the effects of Tofranil and other methods of treatment by means of longitudinal studies

We studied 150 cases (105 cases of endogenous depressions), comparing, like FLEGEL, the results of other therapeutic procedures with those attained with Tofranil. The comparison was carried out between different phases or within the same phase. Moreover follow-up investigations in patients resistant to Tofranil are of interest for the light they throw on the effect of subsequent methods of treatment.

For technical reasons (in conformity with SCHMITT 1960), we distinguished only between successes and failures. More detailed differentiation is not reliable on the evidence of case-histories. We considered treatment to be successful if the patient could resume his place in society. Treatment was judged to be a failure where other therapeutic measures had to be resorted to, even though an improvement was manifested.

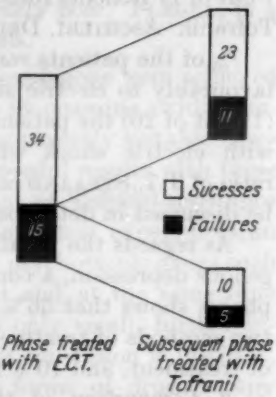


Fig. 2. Comparison of the results of the two methods of treatment in 49 Tofranil-treated patients who had received electro-convulsive therapy (E.C.T.) during a previous depressive phase

The following questions were considered: Does the same patient show a parallel response to treatment in different phases? Do all methods of treatment lead to remission in some patients? Are some patients resistant to all forms of treatment? What is the relationship between the success of treatment achieved with different therapeutic measures? Is, for example, electric shock therapy superior to other procedures? Is Tofranil superior to phenothiazine derivatives?

**1. Comparison of the results of treatment achieved with electric shock and Tofranil.** 49 Tofranil-treated patients had received electric shock therapy in previous phases. Figure 2 gives the results of the two methods of treatment.

As reported by BRUCE et al., *no difference in the success-rates between electric shock and Tofranil* was established. $^2/_3$ of 49 patients had responded favourably to electric shock in a previous phase; $^2/_3$ of the patients of the same group also showed a good response to Tofranil. The graph shows, however, that *for the individual cases the favourable effect of Tofranil does not exactly coincide with that of electric shock.* 46% of the patients showed a good response to both methods of treatment, 22% only to electric shock, and 20% only to Tofranil. 10% were completely resistant to therapy. According to DELAY the incidence of complete resistance is still lower.

The observation that the successes with Tofranil and electric shock only partly coincide explains why better results may be achieved with combined treatment than with one method only (La Loggia, Moore, Kuhn, Schmitt). This does not justify using combination-therapy as a routine procedure.

$^2/_3$ of the patients *resistant to electric shock* (10 out of 15) responded favourably to Tofranil in a later phase. The same result is obtained if the two methods of treatment are compared within the same phase: 7 out of 11 patients resistant to electric shock responded favourably with Tofranil. Aschieri, Delay et al. and Garrett found similar values.

$^2/_3$ of the patients *resistant to Tofranil* (11 out of 16 cases) responded favourably to electric shock in a later phase. Slightly more than half (11 out of 20) the patients resistant to Tofranil were successfully treated with electric shock within the same phase. Bruce et al. found a ratio of 3:7, Straand one of 6:10. Treatment of Tofranil-resistance will be discussed in detail below.

As regards the parallel effect of Tofranil and electric shock in endogenous depression, a comparison of the results of treatment in different phases shows that 56% of the patients show a similar response to the two methods of treatment: 46% responded favourably to both methods of treatment, and 10% failed to respond to either procedure.

**2. Comparison of the results achieved with Tofranil and phenothiazine derivatives within the same phase and in different phases.** 70 of our patients had been previously treated for depression with phenothiazine derivatives (chlorpromazine, levomepromazine, thioridazine). Remission was achieved in 17% (12). These patients were treated in the same phase (30) or in a later phase (40) with Tofranil, a remission being achieved in 63% (44 cases). As an antidepressant drug Tofranil has thus proved to be distinctly superior to the phenothiazine derivatives.

Investigations into the problem whether resistance to phenothiazine runs parallel with resistance to Tofranil show this not to be the case. 60% of the patients with resistance to phenothiazines responded favourably to Tofranil, as opposed to 69% of the group of endogenous depressions who had never received phenothiazines. The difference is not statistically significant. *There therefore appears to be no connection between resistance to Tofranil and resistance to phenothiazines.* This does not, of course, answer the question whether there exists a group of depressive patients who are resistant to all forms of treatment.

**3. Follow-up results of depressive patients with resistance to Tofranil.** 51 patients (36 of whom were suffering from endogenous depression) failing to respond to Tofranil constitute the basis for the following investigation.

Table 10. *Treatment of patients with resistance to Tofranil* (in parentheses: endogenous depressions)

| Treatment | Total | Success | Failure |
|---|---|---|---|
| Electric shock . . . . . | 24 (20) | 13 (11) | 11 (9) |
| Phenothiazine derivatives . . . . | 16 (13) | 3 (1) | 13 (12) |
| Monoamine oxidase inhibitors . . | 12 (11) | 1 (—) | 11 (11) |
| Chlorprothixene . . . . . | 6 (4) | 1 (—) | 5 (4) |

The table shows that the *chances for successful treatment with other drugs in patients resistant to Tofranil are extremely poor*. FLEGEL, in a smaller case-material, reached similar conclusions.

Out of 34 Tofranil-resistant patients only 5 remissions were achieved with other forms of drug-therapy. Even the monoamine oxidase inhibitors appear to fail, and this is also true if apparently suitable cases are selected. Only WALTHER BÜEL reports successful results with these substances. As yet the most effective treatment of Tofranil-resistance appears to be electric shock therapy. From our latest experiences an exception from this rule is occasionally given by psychotropic drugs such as amitriptyline, which exert an antidepressant and at the same time a tranquilizing effect. As our case-material is only small, further investigations are necessary to reveal whether this conclusion is justified. Nevertheless spectacular successes with other forms of drug-therapy in the presence of Tofranil-resistance are definitely excluded. It would therefore be wrong to give up electric shock treatment (CÔTÉ et al.). On the contrary, we agree with FREYHAN (1960) and POGGIALI that it should be resorted to as soon as resistance to Tofranil is evident.

### K. Follow-up investigations

So far 58 patients habe been followed up for a period of 6 months; 41 of these have been observed for as long as 1 year. Controls were carried out 1, 3, 6 and 12 months after withdrawal of treatment or discharge from hospital.

32 of our 58 patients had originally responded to Tofranil; 26 were resistant. 6 months later only 21 of the 32 patients were still at home and capable of work, the other 11 are or were once more in hospital. The fact that $^1/_3$ of the patients treated successfully with Tofranil had to re-enter hospital within 6 months clearly shows that a course of treatment with Tofranil does not preclude relapses (TSCHUDIN). Out of 30 cases examined by DECLICH only 15 had suffered no relapse after 6—7 months. Some of our patients relapsed despite maintenance-treatment with Tofranil. Nevertheless out-patient therapy subsequent to discharge from hospital should not be completely rejected.

Of the 26 depressive patients resistant to Tofranil, one half had resumed their place in society, and the other half was once more in hospital after 6 months. Here again the success-rate corresponds approximately to that achieved with electric shock in the presence of Tofranil-resistance. The findings are summarized in Fig. 3.

After 1 year $^3/_4$ of the patients who had responded favourably to Tofranil, and barely half the patients resistant to Tofranil, had not relapsed. The graphical representation shows that the prognosis in Tofranil-resistant depression which improved spontaneously or under electric shock is no worse than in the other group. The follow-ups are approximately equally favourable in either group, which permits the conclusion that *successful treatment with Tofranil does not diminish the risk of relapse within 6 months.*

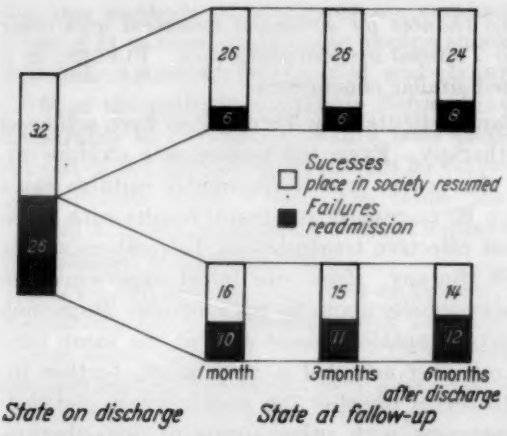


Fig. 3. Endogenous depression: results in patients followed up over a period of 6 months after discharge from hospital

## L. Treatment of blood-relations with Tofranil

It is of particular interest to study the effect of psychotropic drugs in blood-relations. Psychoses with a high family incidence are especially suited to this purpose. In manic-depressive psychosis we may assume that a predisposition, the nature of which is unknown, is inherited (LUXENBURGER). Treatment of blood-relations might provide a means of elucidating the question whether different drugs act merely by virtue of a "symptomatic" effect, e.g. on the clinical picture (regardless of the aetiology), or whether the site of action is a more basic one.

Despite the family incidence of endogenous psychoses, it is naturally difficult to treat an adequately large number of relatives. So far we have not succeeded in obtaining sufficient data for a statistical evaluation. Blood-relations (parents, siblings, children, aunts, uncles and cousins) of 14 of our patients were treated, endogenous psychoses being the indication. Schizophrenia was not excluded, as we were, at the same time, aiming at treating an unselected material in order to examine whether the established nosological classification was of value.

We first tried to establish whether blood-relations showed a pronounced similarity in response to a psychotropic drug. By similarity we

mean that both test-subjects respond in the same favourable or unfavourable manner to the drug. Granted that a similar response has been established, the factors to which this can be attributed must then be examined.

Our present experiences permit the conclusion *that blood-relationship alone cannot be correlated with the response to Tofranil* (see Table 11). Out of 14 related pairs Tofranil had a homogeneous effect in 9 (positive in 6, and negative in 3 pairs), and a heterogenous effect in 5 (positive in one, and negative in the other partner). The degree of kinship appears to play no significant part. Heterogenous responses are established not only between siblings, but also between monozygotic twins.

Table 11. *Treatment of blood-relations with Tofranil*

| Degree of kinship | | Diagnosis | | Results of treatment | |
|---|---|---|---|---|---|
| Mother | Daughter | MDP | MDP | ++ | ++ |
| Sister | Sister | MDP | MDP | ++ | ++ |
| Sister | Sister | MDP | MDP | ++ | ++ |
| Sister | Sister | MDP | MDP | +++ | ++ |
| Sister | Sister | MDP | MDP | + | 0 |
| Niece | Aunt | MDP | MDP | 0 | 0 |
| Nephew | Aunt | MDP | MDP | ++ | ++ |
| Son | Mother | MDP, debility | MDP | ++ | ++ |
| Sister | Sister | MDP, organic features | Involutional depression | 0 | ++ |
| Sister | Brother | Involutional depression | Depressive schizophrenia | ++ | ++ |
| Cousin (fem.) | Cousin (male) | MDP, psychopathy | Schizophrenia | ++ | 0 |
| Mother | Son | Involutional depression | Schizophrenia | ++ | 0 |
| Monozygotic twin sisters | | Depressive schizophrenia | Paranoid schizophrenia | ++ | 0 |
| Father | Daughter | Mixed psychosis | Depressive schizophrenia | ++ | 0 |

Different conclusions are reached if the case-material is grouped according to the diagnosis. Out of 9 pairs suffering from endogenous depression, only 1 responded heterogeneously to Tofranil; in 5 pairs Tofranil had a good effect, in 3 it was a failure. The one exception may be explained by the fact that an organic syndrome was involved in one of the partners, which had an unfavourable influence on prognosis. From our observations we may conclude that *blood-relations suffering from endogenous depression tend to respond in a similar direction to Tofranil* (either positively or negatively).

The question arises whether the similarity in response to Tofranil in endogenous depressions can definitely be attributed to blood-relationship (and thus to constitutional factors), or whether it must be ascribed to other factors. Thus the parallel effect of treatment might, for example, be due to the similarity in the psychopathological picture between blood-relatives. This problem can only be conclusively studied by means of

a statistical evaluation. For the time being our evidence is based on individual observations. These indicate that *the psychopathological picture in blood-relations with endogenous depression often shows a striking similarity.* Physical constitution and premorbid personality structure need not necessarily correspond.

In a female patient involutional depression occurred at the age of 60 and was characterized by a mood of depression and anxiety, lowering of the vital functions, typical daily fluctuations, increased self-observation and the development of pronounced carcinophobia within a period of 3 years. Her brother, who was 4 years younger, developed involutional depression at the age of 50. Here also the clinical picture was one of anxiety and depression, combined with severe primary feelings of guilt and phobic fear of homosexuality, arising within the course of 3 years. Brother and sister responded favourably to treatment with Tofranil, carried out over several weeks with daily doses of 200 mg.

It can hardly be chance that both brother and sister showed the same clinical picture of anxiety and depression with only slight inhibition and with pronounced phobic trends. Only the individual objects of the phobic fear, in one case homosexuality, in the other cancer, appear to have been determined by the premorbid personality structure and the life history.

Two sisters were treated for manic-depressive psychosis. They were both of pyknic constitution, and their premorbid personality was gay and rather conscientious and reserved. Both suffered an attack of depression in the involutional period (having had previous phases) with anxiety but only slight retardation, and with pronounced autonomic disturbances and typical daily fluctuations. During the attacks both sisters grew extremely shy and reserved, and no longer dared to venture out of doors. Both suffered from the fear that their hair might fall out. Tofranil therapy was successful.

Here again the similarity in the basic characteristics of the depression (anxiety, only slight retardation, autonomic disturbances, daily fluctuations, shyness, phobia) can hardly be attributed to chance. The content of phobic fear is explained by the fact that two brothers were bald before the age of 30, thus attracting much notice. This does, however, not account for the presence of phobic trends in both the sisters. Numerous examples of similar psychopathological pictures in blood relations could be given, depressive pictures with atypical symptoms being particularly striking. It is impressive that *blood-relations with atypical pictures also show a similarity in response to Tofranil.* In view of the accepted notion that Tofranil exerts its optimum effect in inhibited forms of depression, its action might be expected to be less reliable in atypical pictures, and therefore also less uniform in blood-relations. This is, however, not the case.

Moreover it is important that classical forms of endogenous depression, with inhibition of vital functions, pronounced retardation and apathy, primary feelings of guilt and typical daily fluctuations, occasionally not only fail to respond to Tofranil, but that blood-relations react in a similar direction:

The patient and her aunt suffered from purely depressive recurrent manic-depressive psychosis. Despite a different physical constitution, their premorbid personality showed many similarities: a syntonic-gay, extrovert, active and conscientious character. In both cases the depressive picture was of the inhibited type, with lack of drive, retardation, primary feeling of guilt, feelings of insufficiency and typical aggravation of the symptoms in the mornings. Each patient, without the knowledge of the other or of the other's physician, was given Tofranil. The niece failed to respond to parenteral, and the aunt to oral treatment. In both cases the drug had to be withdrawn after 2 weeks on account of the same side-effects, i.e. pronounced somnolence necessitating complete confinement to bed, the severe state of depression being unchanged. Electric shock had a prompt effect in both cases.

Why Tofranil may prove a failure even in classical cases has not yet been discovered. *Tofranil-resistance in blood-relations indicates that an unknown, possibly hereditary factor*, which would appear to be linked with the inherited disposition to the illness, *may be involved*. Our observations also speak against the simplifying assumption that Tofranil has a merely "symptomatic" effect on the depressive state. The positive action of the drug, as well as its failure, appear to be dependent not on the clinical condition alone, but also on other factors, most probably of a hereditary nature.

Our last example demonstrates that certain side-effects, and even relatively rare manifestations, may be correlated in blood-relations. Possibly this is not a chance occurrence. *On the whole, however, no correlation between side-effects among blood-relations can be established.*

Repeatedly hopes have been raised (SCHMITT) that the established nosology might become questionable in the light of modern psychotropic treatment. Our present experiences do not yet permit the introduction of new and fruitful points of view into diagnosis. The results achieved in the treatment of blood-relations suffering from different forms of psychosis speak in favour of strict adherence to the old nosological classification. In contrast to blood-relations with endogenous depression, blood-relations suffering from endogenous psychoses of different aetiology responded with complete irregularity to Tofranil. We even attempted to treat 3 patients with schizophrenia without depressive features with Tofranil, as their relatives had responded favourably to the drug. All 3 completely failed to respond, and did not even show side-effects.

Moreover our results achieved in the treatment of monozygotic twins suffering from schizophrenia are remarkable:

The twin sisters, aged 67, lost their father at the age of 1, and were brought up by a step-father in the country. After having worked as maids they both got married at the age of 29; they had no children. One twin (A) developed chronic schizophrenia of the paranoid type with depressive trends at the age of 40. The picture was first characterized by depression, to which were added in the course of time ideas of persecution, hallucinations and obsessional symptoms. At the age of 57 the patient spent a short time in hospital. In the last 10 years the severe paranoid psychosis has continued unchanged.

In the other twin (B) the first attack occurred at the age of 56. From the beginning it was a certain case of schizophrenia of the paranoid type. In both twins the paranoid ideas were primarily concerned with imaginary persecution by the neighbours. In patient B the psychosis took a slightly undulating course, and gave rise to 4 transient periods in hospital. The clinical picture of depression and anxiety responded favourably to Tofranil. In the intervals pronounced schizophrenic personality disorders were invariably present. This twin (B) also showed obsessive symptoms (scratching). At her fifth stay in hospital depression and inhibition predominated, and the patient was successfully treated with Tofranil. In view of the result, Tofranil was administered to twin A, suffering from manifest paranoid symptoms; but, as was be expected, the clinical condition was not changed.

Thus in the one twin the mood of depression and inhibition could be successfully treated with Tofranil, the schizophrenic symptoms in both twins being unchanged. This once more proves that the effect of Tofranil is primarily direct towards the emotional sphere.

## Summary

200 patients suffering from depression of varying origin were treated with Tofranil (imipramine). 105 in-patients with endogenous depression formed the nucleus for an examination of the factors which may modify the mode of action of the drug. In addition to longitudinal and cross-section studies the results of treatment of psychotic blood-relations were studied. The results may be summarized as follows.

In endogenous depression and depressive-schizophrenic mixed psychoses Tofranil proved to be successful in $^2/_3$ of the cases. The majority of the patients were able to resume their place in society; in 16% of the cases of endogenous depression freedom from symptoms was achieved.

Table 12 gives a survey of the factors examined and of their influence on the results of treatment. The good effect of Tofranil is prejudiced in recurring attacks, in phases of more than 1 year's duration, and if the

Table 12. *The relationship of various factors to the result of Tofranil treatment*

| | Not influencing therapeutic results | Influencing therapeutic results |
|---|---|---|
| Patient-related factors *not* primarily related to the disease | Age<br>Sex<br>Constitution<br>Premorbid personality, intelligence<br>Family incidence of endogenous psychosis | None |
| Patient-related factors *primarily related to the disease* | Age at first attack<br>Differential diagnosis: MDP — involutional depression<br>Anxiety<br>Depression of vital functions<br>Primary feelings of guilt<br>Tendency to suicide<br>Reactive factors<br>Schizophrenic trends | Hereditary disposition*<br>Number of phases<br>Course of psychosis<br>Duration of phases<br>Inhibition, lack of drive<br>Agitation<br>Delusional ideas (depressive)<br>Autonomic symptoms<br>Organic features |
| *Drug-related* factors | — | Mode of administration*<br>Dosage*<br>Side-effects* |

* Not statistically verified.

illness has not taken the classical cyclic course. The changes for successful treatment are less in the presence of agitation, depressive delusional ideas and organic involvement. Parenteral administration is slightly superior to oral; moreover, daily doses of 200 mg are more effective than lower doses. The presence of side-effects appears to favour the prognosis. The best results are achieved in endogenous depression with inhibition and lack of drive. Autonomic symptoms increase the chances for success; all the other factors examined (see Table 12) do not influence the results of treatment.

Longitudinal studies in endogenous depression showed Tofranil treatment to be equal to electric shock therapy. As the favourable effect only partly coincides in the individual patients, the two methods of treatment cannot replace each other. 20% of the patients respond to only one of the two procedures; 10% are resistant to either form (a part of which show spontaneous remissions). In patients resistant to the one method of treatment, remissions may still be achieved with the other.

At present Tofranil (plus psychotherapy and social guidance) constitutes the method of choice for initiation treatment in endogenous depression with lack of drive. In agitated forms of depression, the adjunction of a phenothiazine derivative is recommended. If Tofranil should prove to be a failure in an in-patient, it is advisable to resort immediately to electric shock treatment, without giving further drugs

a trial. As a rule endogenous depressions with resistance to Tofranil do not respond to other drugs either. An exception may be given by amitriptyline.

Follow-up studies reveal that a completed course of treatment with Tofranil does not diminish the risk of relapse.

Treatment of blood-relations with Tofranil shows that the established nosological classification still holds true. The large majority of endogenous depressions shows a similarity in response to Tofranil. In part the parallel response may be explained by the similarity in the psychopathological aspects of the clinical picture in blood-relations. Possibly an unknown hereditary factor is also involved, since atypical forms of depression also respond in the same (positive or negative) sence to Tofranil.

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# Die Beziehungen von Lernvermögen und Spontanmotilität alternder Ratten unter Behandlung mit Natrium-Pentamethylenhydroxybutyrat

Von

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Mit 2 Textabbildungen

*(Eingegangen am 11. Dezember 1960)*

In früheren Untersuchungen konnten Dentzer und Enders den Befund von Verzàr-McDougall bestätigen, daß junge Ratten im Labyrinthlernversuch schneller lernen als alte. Ferner gelang es, durch Applikation von Natrium-Pentamethylenhydroxybutyrat die Lernleistungen alter Tiere denen junger Tiere anzugleichen. Die Leistung junger Tiere dagegen wurde durch die Behandlung mit Natrium-Pentamethylenhydroxybutyrat nicht verbessert.

Im Labyrinthlernversuch soll das Tier erlernen, den Irrgarten auf dem kürzesten Weg zum Futterplatz zu durchlaufen. Hierdurch wird das Tier auf eine bestimmte Reaktionsfolge geprüft, die zur Beurteilung des psychomotorischen Gedächtnisses dient. Nach Dembowski soll es sich beim Labyrinthversuch um die Prüfung eines komplexen, bedingten Reflexes handeln, der sich aus einer aufeinanderfolgenden Reihe von Einzelreizen ergibt. Nach Ausbildung der Einzelreflexe im Verlauf des Lernversuches löst schließlich das Aufsetzen des Tieres auf den Startplatz das Ablaufen der Reflexkette aus.

Nach Witt wird die Spontanmotilität durch zwei völlig verschiedene Faktoren bestimmt, die Motorik und die Spontaneität.

Der Lerneffekt im Labyrinthlernversuch, nach dem obengenannten also die Ausbildung eines komplexen, bedingten Reflexes, ist aber sicher abhängig von der Spontaneität, d.h. dem inneren Antrieb der Tiere, die ihnen gestellte Aufgabe zu lösen.

Wir wollten deshalb prüfen, ob auch die Ausbildung einfacher bedingter Reflexe durch Natrium-Pentamethylenhydroxybutyrat beeinflußt wird. Wir hielten die Fluchtreaktion von einem elektrischen Stromfeld für diesen Zweck geeignet, da diese Versuchsanordnung das Tier in eine akut bedrohliche Situation bringt und somit die Spontaneität weitgehend ausschaltet.

Da Natrium-Pentamethylenhydroxybutyrat als Modell einer neuen Substanzgruppe (Enders *et al.*) zentralerregende Wirkungen besitzt, von

anderen zentralerregenden Körpern wie den Phenylalkylaminen aber bekannt ist, daß sie gleichzeitig Spontanmotilität und Hungergefühl beeinflussen, untersuchten wir, ob dem Natrium-Pentamethylenhydroxybutyrat ähnliche Wirkungen zukommen. Durch vergleichende Untersuchungen sollte Aufschluß darüber gewonnen werden, ob eine zentrale Erregung zwangsläufig eine Erhöhung der Spontanmotilität zur Folge hat und in wieweit zentrale Anregung und Depression des Hungergefühls gekoppelt sind.

## Methodik

### *1. Ausbildung bedingter Reflexe*

Wir verwendeten eine Modifikation der Sprungkäfigmethode nach Warner, bei der Ratten in einen zweigeteilten Käfig gegeben werden, dessen beide Hälften durch eine kleine Öffnung miteinander verbunden sind. Der Boden der beiden Teilkäfige ist wechselseitig elektrisch aufladbar, so daß die Tiere elektrischen Stromstößen ausgesetzt werden können. Zur Aufladung der Stromfelder wurde ein Weidezaungerät[1] verwendet. Die Stromstöße wurden mit einer Frequenz von 60/min und mit einer Spannung von 9 Volt verabreicht.

Der Versuch lief nach folgendem Schema ab:

1. Akustisches Signal in der linken Käfighälfte (hoher Ton) über 5 sec. Der Ton wurde durch eine Klingel mit 91 Phon ausgelöst.
2. Aufladung des linken Stromfeldes über 10 sec.
3. Akustisches Signal in der rechten Käfighälfte (tiefer Ton) über 5 sec. Der Ton wurde durch eine elektrische Signalhupe mit 85 Phon erzeugt.
4. Aufladung des rechten Stromfeldes über 10 sec, usw.

Ein Einzelversuch, bei dem von jedem Tier 10 Wechsel verlangt wurden, dauerte also $2^1/_2$ min.

Wenn im späteren Verlauf des Versuchs die Tiere gelernt hatten, auf akustisches Signal zu wechseln, unterblieb das Aufladen des soeben verlassenen Stromfeldes, da wir in Vorversuchen beobachtet hatten, daß ein fehlerhafter Rücklauf der Tiere auf das noch geladene Stromfeld zu einer starken Irritierung führte, die den Versuchsverlauf beeinträchtigte.

Der Hauptversuch erstreckte sich über 26 Tage. Jedes Tier kam zweimal täglich in den Versuch und erhielt 30 min vor Versuchsbeginn 2 mg/kg Natrium-Pentamethylenhydroxybutyrat oder 0,2 ml NaCl-Lösung/100 g subcutan appliziert. Der Abstand der beiden Injektionen betrug 5 Std, die injizierte Flüssigkeitsmenge 0,2 ml/100 g Körpergewicht. Nach den in vorhergehenden Versuchen gemachten Erfahrungen wurden die Tiere (AB) über 4 Tage mit zweimal 2 mg/kg Natrium-Pentamethylenhydroxybutyrat subcutan vorbehandelt.

[1] Firma Horizont-Gerätewerk Dr. H. Müller, Korbach.

Wir benutzten weibliche Wistar-Ratten. Die verwendeten 14 jungen Tiere (JU) waren 10—12 Wochen alt und hatten ein Gewicht von 100 bis 120 g (Gruppe J). Die alten Tiere waren im Alter von 20—25 Monaten und hatten ein Gewicht von 300—380 g. Die 14 jungen (JU) wie auch 14 alten Ratten (Gruppe AU = alt, unbehandelt) erhielten zweimal täglich 0,2 ml NaCl-Lösung/100 g subcutan injiziert. Weiteren 14 alten Ratten (Gruppe AB = alt, behandelt) wurden zweimal täglich 2 mg/kg Natrium-Pentamethylenhydroxybutyrat in 0,2 ml/100 g subcutan appliziert.

*2. Messung der Spontanmotilität*

a) Wegen der Einwände gegen die viel verwendete Zitterkäfigmethode bestimmten wir die Spontanmotilität in Anlehnung an die Methode von Dews durch Unterbrechung eines Infrarotstrahls. Es wurden die in Abschnitt 1 genannten Ratten und männliche Mäuse im Gewicht von 18—22 g verwendet. Gruppen zu je 5 Tieren wurden für 30 min in einen Kasten gegeben und die Anzahl der Infrarotstrahlunterbrechungen registriert.

b) Wir verwendeten eine Modifikation des von P. Kneip zur Registrierung sedativer Wirkungen angegebenen Klettertests. In Vorversuchen stellten wir fest, daß sich diese Versuchsanordnung auch zur Testung zentralerregender Substanzen eignet. Als Versuchstiere dienten männliche Mäuse im Gewicht von 18—22 g. Als Maß der Kletteraktivität bestimmten wir, wie oft innerhalb von 10 min von den Mäusen der obere Käfigrand erreicht wurde (Käfigmaße: $27 \times 23 \times 17$ cm).

*3. Bestimmung des Hungergefühls*

Als Versuchstiere verwendeten wir männliche Ratten im Gewicht von 180—200 g, die in Einzelkäfigen gehalten wurden. In Vorversuchen wurde festgestellt, daß die Tiere bei einer täglichen Futterzuteilung von 20 g Gewichtskonstanz zeigten. Als Futter verwendeten wir folgende Zubereitung: 1,000 kg Magermilchpulver, 0,150 kg Lebertran, 0,150 kg McCollum-Salz, 0,300 kg Bierhefe und 5,000 kg Haferflocken auf 20 Liter Wasser.

Wir beobachteten durch Kontrollen im Abstand von 30 min, nach welcher Zeit die Ratten ihre Futterration verzehrt hatten. In wöchentlichem Wechsel erhielten die Tiere täglich NaCl-Lösung subcutan, 2 mg/kg Natrium-Pentamethylenhydroxybutyrat subcutan und 2 mg/kg Amphetamin subcutan injiziert. Die applizierte Flüssigkeitsmenge betrug jeweils 0,2 ml/100 g Körpergewicht.

Nach Abschluß des Versuchs wurde die durchschnittliche Zeit, die täglich zum Verzehr des Futters notwendig war, bestimmt.

## Ergebnisse

### *1a. Die Ausbildung unbedingter und bedingter Reflexe an jungen und alten Ratten*

Wie aus den Tabellen 1a und 1b zu ersehen ist, zeigten sich bei der Ausbildung einfacher unbedingter und bedingter Reflexe junge Tiere den alten überlegen.

Tabelle 1a. *Ausbildung der unbedingten Reflexe*

Zahl der Ratten, die jedesmal nach Aufladen des Stromfeldes innerhalb 10 sec wechselten (Gesamtzahl aus beiden Versuchen pro Tag)

JU = junge unbehandelte Tiere; AU = alte unbehandelte Tiere; AB = alte behandelte Tiere.

| Gruppe | 1. | 3. | 6. | 9. | 12. | 15. | 18. | 21. | 24. |
|---|---|---|---|---|---|---|---|---|---|
| | Versuchstag | | | | | | | | |
| JU 14 Tiere . | 4 | 11 | 13 | 16 | 18 | 21 | 24 | 23 | 24 |
| AU 14 Tiere . | — | 2 | 6 | 12 | 16 | 18 | 19 | 20 | 22 |
| AB 14 Tiere . | 6 | 12 | 16 | 21 | 24 | 25 | 24 | 26 | 26 |

Tabelle 1b. *Ausbildung der bedingten Reflexe*

Zahl der Ratten, die während der täglich durchgeführten Versuchsperioden ohne Fehler auf akustisches Signal vor Stromfeldaufladung wechselten.

| Gruppe | 1. | 3. | 6. | 9. | 12. | 15. | 18. | 21. | 24. |
|---|---|---|---|---|---|---|---|---|---|
| | Versuchstag | | | | | | | | |
| JU 14 Tiere . | — | — | — | 2 | 2 | 6 | 7 | 11 | 16 |
| AU 14 Tiere . | — | — | — | — | 2 | 2 | 4 | 7 | 11 |
| AB 14 Tiere . | — | — | 1 | 4 | 5 | 15 | 10 | 18 | 19 |

Am 3. Tag des Versuches wechselten z. B. (Tabelle 1a) aus der Gruppe der alten unbehandelten Tiere (AU) 2 von 14 Tieren, aus der Gruppe der jungen Tiere (JU) dagegen 11 von 14 Tieren nach Aufladung des Stromfeldes in den anderen Käfig über. Am 15. Tag reagierten (Tabelle 1b) 6 von 14 Tieren der Gruppe JU auf akustisches Signal gegenüber 2 Tieren der Gruppe AU.

### *1b. Beeinflussung der Ausbildung bedingter Reflexe an alten Ratten durch Natrium-Pentamethylenhydroxybutyrat*

Auf Abb. 1 ist der Verlauf der Ausbildung bedingter Reflexe von alten behandelten Tieren (AB) und alten unbehandelten Tieren (AU) dargestellt. Der Kurvenverlauf gibt die Mittelwerte der Reaktionen auf akustisches Signal wieder. Während z. B. am 6. Tag der Mittelwert der

Gruppe AU bei 1,6 lag, erreichte die Gruppe AB im Mittel 4,5. Im weiteren Verlauf des Versuches nähern sich — wie bei derartigen Dressurversuchen nicht anders zu erwarten — die Werte einander (Tabelle 2).

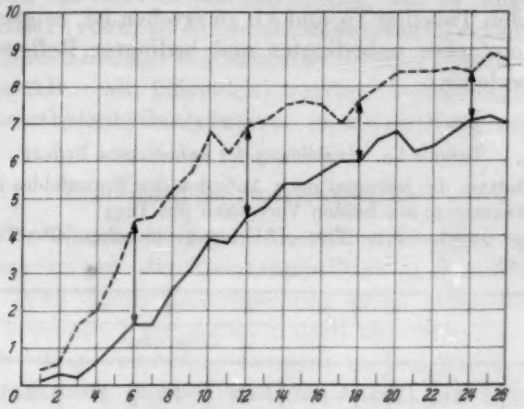


Abb. 1. Ordinate: Mittelwerte der Reaktionen auf akustischen Reiz. Abszisse: Versuchstage. ——— Gruppe AU; — — — — Gruppe AB. Die Mittelwerte ergeben sich aus der Summe der positiven Reaktionen der einzelnen Tiere in beiden täglich durchgeführten Versuchen und deren Division durch 28

Tabelle 2

| Versuchstag | Differenz der Mittelwerte der Reaktion auf akustischen Reiz (Gruppe AU und AB) | Signifikanz $k =$ |
|---|---|---|
| 6. | 2,9 | 5,2 |
| 12. | 2,4 | 2,9 |
| 18. | 1,5 | 1,68 |
| 24. | 1,3 | 1,33 |

$k$ = mittlerer Fehler der Differenz zweier Mittelwerte.

### *2. Die Wirkung von Natrium-Pentamethylenhydroxybutyrat auf die Spontanmotilität*

Wie aus Tabelle 3 und Abb. 2 zu ersehen ist, konnten wir sowohl bei Mäusen als auch bei jungen und alten Ratten in den bei den Dressurversuchen verwendeten Dosen von 2 mg/kg Natrium-Pentamethylenhydroxybutyrat subcutan keine Steigerung der Spontanmotilität beobachten. Da wir in den Dressurversuchen die Tiere über 4 Tage täglich zweimal mit 2 mg/kg Natrium-Pentamethylenhydroxybutyrat vorbehandelt hatten, applizierten wir sowohl Mäusen als auch jungen und alten Ratten über mehrere Tage gleiche Dosen. Jedoch auch nach Vorbehandlung über 7 Tage konnten wir keine Motilitätssteigerung nach Applikation von Natrium-Pentamethylenhydroxybutyrat konstatieren. Ganz im Gegenteil kam es sowohl bei den vorbehandelten als auch bei

Tabelle 3. *Spontanmotilität gemessen mit der Methode nach* DEWS *(im Mittel 7 Versuche)*.

Als Versuchstiere dienten männliche Mäuse im Gewicht von 17—22 g und weibliche Ratten im Gewicht von 80—100 g und 300—380 g

| Substanz | Zahl der Infrarotstrahlunterbrechungen innerhalb von 30 min | | |
|---|---|---|---|
| | Mäuse | Ratten jung | Ratten alt |
| NaCl-Lösung 0,2 ml/100 g subcutan | 265 | 60 | 79 |
| Natrium-Pentamethylenhydroxybutyrat 2 mg/kg in 0,2 ml/100 g subcutan | 183 | 65 | 62 |
| Amphetamin 2 mg/kg in 0,2 ml/100 g subcutan | 1213 | 335 | 317 |
| | Nach Vorbehandlung über 7 Tage | | |
| NaCl-Lösung 0,2 ml/100 g subcutan | 269 | 84 | 104 |
| Natrium-Pentamethylenhydroxybutyrat 2 mg/kg in 0,2 ml/100 g subcutan | 175 | 88 | 79 |

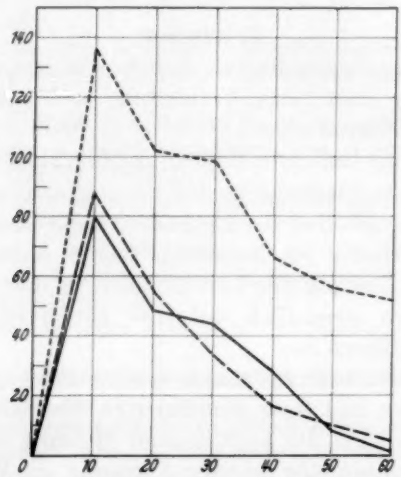


Abb. 2. *Spontanmotilität im Klettertest nach* P. KNEIP. Für eine Substanz verwendeten wir 6 Gruppen zu je fünf männlichen Mäusen im Gewicht von 18—22 g. Ordinate: Ausmaß der Klettertätigkeit. Häufigkeit des Erreichens des oberen Käfigrandes innerhalb 10 min. Abszisse: Zeit in Minuten. ——— NaCl-Lösung subcutan (0,2 ml/20 g Maus); — — — — Natrium-Pentamethylenhydroxybutyrat subcutan 2 mg/kg (0,2 ml/20 g Maus); ..... Amphetamin subcutan 2 mg/kg (0,2 ml je 20 g Maus)

den nicht vorbehandelten Tieren mit Ausnahme der jungen Ratten in der Dewsschen Versuchsanordnung zu einem leichten, jedoch nicht signifikanten Absinken der Spontanmotilität.

In Bestätigung früherer Befunde anderer Autoren (HAAS und ZIPF, HAFFNER, HAUSCHILD, MALORNY, ROTHLIN und CERLETTI, SCHULTE

et al., TRIPOD, WATERMAN) führte Amphetamin sowohl bei Mäusen als auch bei jungen und alten Ratten zu einem starken Anstieg der Spontanmotilität.

*3. Beeinflussung des Hungergefühls*

Die Versuche wurden an männlichen Ratten im Gewicht von 180 bis 200 g durchgeführt.

Tabelle 4

| Substanz | Dosis | Freßzeit min |
|---|---|---|
| NaCl-Lösung . . . . . | 0,2 ml/100 g | 41 |
| Natrium-Pentamethylenhydroxybutyrat | 2 mg/kg in 0,2 ml/100 g subcutan | 40 |
| Amphetamin . . . . . | 2 mg/kg in 0,2 ml/100 g subcutan | 71 |

Wie aus Tabelle 4 ersichtlich, beeinflußte Natrium-Pentamethylenhydroxybutyrat in den verwendeten Dosen das Hungergefühl nicht. Amphetamin dagegen wirkte, wie auch ENDERS in Bestätigung anderer Autoren zeigen konnte, stark appetithemmend.

## Diskussion

Die Ausbildung eines bedingten Reflexes beruht nach DEMBOWSKI auf der Entstehung einer neuen Verbindung in den Nervenzentren, die als Assoziation bezeichnet wird.

Da die Ausbildung bedingter Reflexe an alten Ratten durch Natrium-Pentamethylenhydroxybutyrat in der Sprungkäfigmethode, einer Anordnung, in der der Einfluß der Spontaneität auf den Versuchsverlauf weitgehend ausgeschaltet ist, begünstigt wurde, kann geschlossen werden, daß die Verbesserung der Lernfähigkeit in den oben angeführten Labyrinthversuchen wesentlich auf eine Erhöhung der assoziativen Leistung zurückzuführen ist.

Natrium-Pentamethylenhydroxybutyrat erhöht, gemessen mit der Methode von DEWS und einer modifizierten Methode nach KNEIP die Spontanmotilität nicht. Da nach unserer Meinung eine Erhöhung der assoziativen Leistungen eine zentrale Anregung zur Voraussetzung hat, ergibt sich, daß zentrale Anregung und Erhöhung der Spontanmotilität nicht zwangsläufig gekoppelt sind.

Weiterhin zeigten die Untersuchungen, daß Natrium-Pentamethylenhydroxybutyrat in zentralanregenden Dosen zu keiner Beeinflussung des Hungergefühls führt.

## Summary

The response rate in conditioned reflexes in aged rate is augmented by sodium $\beta\,\beta$-pentamethylene-$\gamma$-hydroxybutyrate.

Doses of sodium $\beta\,\beta$-pentamethylene-$\gamma$-hydroxybutyrates stimulating the central nervous system, neither enhance spontaneous motor activity nor depress appetite.

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Psychopharmacologia 2, 416—424 (1961)

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# Some Effects of Adiphenine, Benactyzine, and Chlorpromazine upon Several Operant Behaviors*

By

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With 4 Figures in the Text

*(Received May 1, 1961)*

The value of using several behavioral procedures in assessing drug effects has already been demonstrated. DEWS (1955) has reported, for example, that some doses of pentobarbital may show a clear depressive effect on fixed interval behavior but no effect on fixed ratio behavior. He has also reported that a simple discrimination procedure may indicate that a drug has no effect upon discriminations although a more complex procedure will show profound changes in discriminations (DEWS, 1956). While studying the effects of reserpine upon aversively-controlled behavior, BRADY (1956) demonstrated that reserpine will greatly reduce the conditioned suppression of behavior when generated by an "anxiety" procedure but will cause no reduction when generated by a punishment procedure.

While the different results with different behavioral procedures may sometimes be explained after the experiments, it is difficult to predict the results in advance. The studies reviewed above have shown that a compound may have quite different effects upon relatively similar types of behavior. It appears, then, that behavior exists in multiple forms, each of which can exhibit a different sensitivity to a drug. For this reason, the behaviors generated by four different procedures have been selected for this study. Two involve positive reinforcement with a time discrimination in one and not the other, while the other two deal with different aspects of negative reinforcement with electric shock. While they represent only a few of the available possibilities, the procedures taken together should permit a more accurate definition of the drugs' actions.

In this study three compounds, benactyzine or "Suavitil", chlorpromazine or "Thorazine", and adiphenine or "Trasentine", were studied for their behavioral effects. Benactyzine and chlorpromazine have in common the fact that both are used in the treatment of psychiatric patients, while benactyzine and adiphenine were compared because of their closely related chemical structures.

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* A slightly modified version of this paper was presented at the 1956 fall meetings of the American Society for Pharmacology and Experimental Therapeutics.

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## Apparatus

The basic apparatus consisted of a metal box containing a microswitch lever and a motor-driven dipper for delivering a small quantity of water to the animals. The floor of the box was constructed of metal rods through which an aversive electric shock could be administered. Cam-driven microswitches scrambled the polarity of each rod in the grid floor during a shock so that the animal could not avoid the shock by standing on two rods of the same polarity.

The procedures to be described below were programed and recorded automatically by relays, timers, counters, cumulative recorders, and associated equipment. In order to prevent equipment sounds from affecting the animals, a random "white" noise was presented in the experimental room and the equipment was placed in a separate room.

## Experiment I

*Fixed interval reinforcement.* The subjects, about eight months old at the beginning of this experiment, were two male albino rats from the Charles River Sprague-Dawley strain. After 32 hours of water deprivation, they were conditioned to press the lever by a continous reinforcement schedule (i.e., each lever press produced the water reinforcement). Then the fixed interval schedule of reinforcement was adopted whereby the first lever-press after two minutes was reinforced. This training was continued for approximately 300 hours to insure that the final stable pattern of performance had developed. The pattern involved a long pause after a reinforcement and then a positive acceleration of the response rate as the time for reinforcement approached (see control record of Fig. 1). The pause after the reinforcement indicated that the animal had acquired a temporal discrimination.

Benactyzine and chlorpromazine were administered to each animal in several doses ranging from 1 to 3 mg/kg of chlorpromazine and 0.5 to 8 mg/kg of benactyzine. Adiphenine was tried at 8—16 mg/kg.

Injections were made intraperitoneally 10 minutes before an experimental session. The total duration of the experimental session was approximately 16 hours, but since the animals usually satiated within three hours, only the first two hours were used in the quantitative analysis of the results. Each drug session was followed by one or more control sessions in which either saline was injected or no injection was made. Saline, however, had no effect. Since at least four days elapsed between a drug session and a control session and since drugs were never administered more frequently than once a week, carry-over effects from one session to another were not observed.

Benactyzine, over the entire dose range studied (0.5—8 mg/kg), increased the over-all rate of responding. However, close study of the

cumulative record showed that two different patterns of responding were correlated with the increased rate. The two patterns can be seen in Fig. 1 where representative cumulative records for one animal are shown. Pattern 1: the pause after the reinforcement disappeared; the animal responded indiscriminately at a low rate throughout the two-minute period. Note that the terminal rate at the end of the interval was much lower than normal. This pattern tended to occur at the moderate to high doses (2—8 mg/kg) and may be seen most clearly in Fig. 1 for the first hour following 8 mg/kg. Since responses occurred early in the post-reinforcement period, where under control conditions no responses appeared, the over-all rate was increased slightly. This pattern may be described as a disruption of the temporal discrimination. Pattern 2: the pause after the reinforcement was maintained, but it was much briefer than under control conditions. As a result, the rate accelerated to a high value and was maintained until the next reinforcement. During this phase of the action of benactyzine, the over-all rate was increased markedly. This pattern tended to occur at low doses (0.5—1.0 mg/kg) or at higher doses during the second hour following Pattern 1 and may be considered a type of stimulant action. In general, the duration of action of benactyzine was less than two hours.

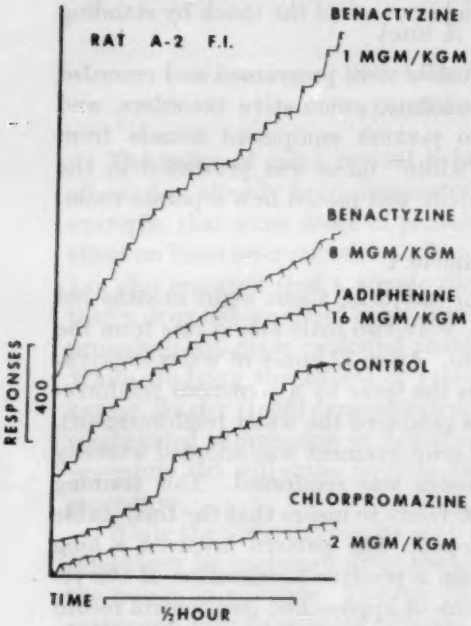


Fig. 1. The effects of adiphenine, benactyzine, and chlorpromazine upon fixed interval behavior. Typical cumulative response curves are shown in which deflections of the pen indicate reinforcements

When chlorpromazine was studied in the same animals, the effect was to reduce drastically the over-all rate of responding. As shown in the lower record of Fig. 1, the animals tended to pause longer after a reinforcement and to emit fewer responses at the end of the two-minute interval. No signs of disruption of the temporal discrimination (Pattern 1 described above) were in evidence.

Adiphenine, in doses of 8—16 mg/kg, produced very little change in the typical fixed interval behavior. Although larger doses were not tried

(to avoid the possibility of toxicity), it was clear that adiphenine was inactive at dose levels which would have produced marked effects with the structurally similar benactyzine.

## Experiment II

*Variable Interval Reinforcement.* The same compounds were studied in a second behavioral test, that differed from the first primarily in the scheduling of the reinforcement. In this case the reinforcement was made available after variable intervals of time randomized around a mean of 30 seconds. The final performance which developed under this procedure was a more or less steady rate of responding which did not display the special temporal patterning characteristic of the fixed interval schedule. Four rats, under 23 hours water deprivation, were observed during 75-minute sessions. This experiment, like Experiment 1, used a crossover design where each animal served as his own control and received each drug in a number of doses. Drugs were injected intraperitoneally in a manner similar to that described in Experiment 1.

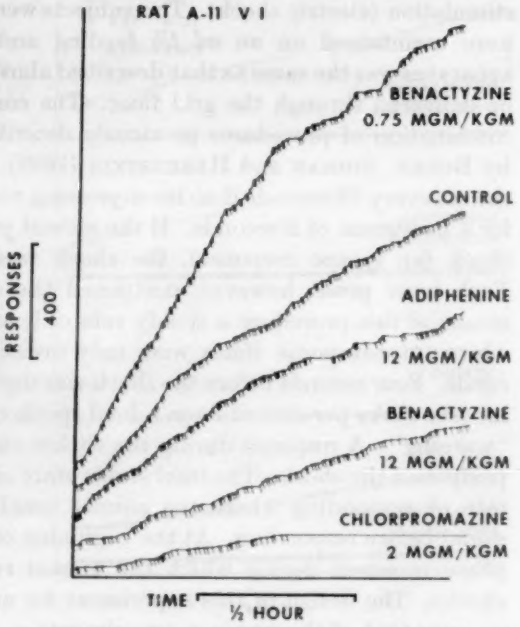


Fig. 2. The action of three drugs upon variable interval responding

Benactyzine was given with a dosage range from 0.25 to 12 mg/kg. The data for a typical animal are shown in Fig. 2. With medium to high doses (2—12 mg/kg) the usual effect was to decrease the rate of responding. Thus, at these doses the compound might be described as a "depressant", and the effect is consistent with the low rate seen in Pattern 1 of the fixed interval experiment. Upon some occasions, however, an early rate increase occurred during the first half hour of the session. This "stimulant" activity was seen more often with low doses (less than 1 mg/kg) but was a somewhat variable affair.

Chlorpromazine, administered to the same animals in doses of 1—2 mg/kg, produced a simple and marked decrease in the response

rate. In many cases (as is shown in Fig. 2) the rate dropped to zero before the end of the session. Adiphenine produced no change with doses up to 12 mg/kg.

### Experiment III

*Free Operant Avoidance.* Unlike the previous experiments, this procedure involved control of the lever-pressing behavior by aversive stimulation (electric shock). The subjects were six male albino rats who were maintained on an *ad lib* feeding and watering schedule. The apparatus was the same as that described above except that a shock could be delivered through the grid floor. The conditioning procedure was a combination of procedures previously described by SIDMAN (1955) and by BOREN ,SIDMAN and HERRNSTEIN (1959). A shock was delivered to the rat every 16 seconds if no lever-pressing response occurred, and lasted for a maximum of 2 seconds. If the animal pressed the lever during the shock (an escape response), the shock was terminated immediately. Each lever press, however, postponed the shock for 20 seconds. By means of this procedure a steady rate of lever-pressing was conditioned where inter-response times were only occasionally greater than 20 seconds. Four seconds before the shock was due, a clicking auditory stimulus (six clicks per second from a loud speaker) came on to give an extra "warning". A response during the clicker cut off the stimulus and also postponed the shock. The final stable state of the behavior was a steady rate of responding where the animal usually waited for the warning signal before responding. At the beginning of each session a "warm-up" phase occurred during which the animal received a large number of shocks. The design of this experiment for administering drugs was the same as that of the previous experiments.

The action of benactyzine, studied through a dose range of 0.5 to 12 mg/kg, was a decrease in the early session warm-up phase (i.e., the animal responded more frequently to the warning signal). Typical data may be seen in Fig. 3. Occasionally an increased rate was seen for 30 minutes or so, but effects of the drug were not apparent at any later time. Even though doses as large as 12 mg/kg were tried, a rate decrease was not observed, in contrast to the previous two experiments. The main action of benactyzine upon avoidance behavior, then, was to exert a brief "stimulating" effect. In view of SIDMAN's discovery (1955) that well trained rats may not be affected by the warning stimulus but instead respond on the basis of a temporal discrimination, the possibility that this action of benactyzine may be due, at least in part, to a disruption of the temporal discrimination cannot be ruled out. Other workers, using a different avoidance technique, have also reported a type of stimulant activity upon avoidance behavior (JACOBSEN and SONNE 1955).

Chlorpromazine produced a prolonged depressive action on the avoidance behavior. In general, doses of 1—3 mg/kg greatly decreased the probability of a response to the warning stimulus. This effect may be clearly seen in Fig. 3 by observing the large number of shocks that the animal received throughout the session. In the dose range of 1—3 mg/kg, the animals were still able to maintain escape responding to the shock at the usual control probability (in fact, the escape behavior plus rapid responding just after the shock maintained the over-all rate of responding at a spuriously high level). This would indicate that the depressant effect upon avoidance responding was not due simply to anesthesia or a motor incapacity. Other studies where the dose was increased above this range, however, showed that escape responding could be depressed.

The highest dose of adiphenine tried was 12 mg/kg. The compound was inactive in this test as in the others.

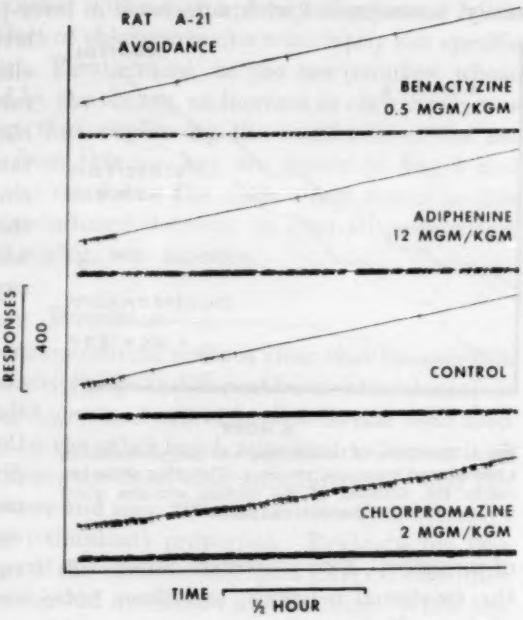


Fig. 3. A comparison of the effects of three drugs on avoidance responding. The pen deflections on the cumulative record indicate shocks, while the deflections of the lower line mark the onset of the warning signal

## Experiment IV

*Conditioned Emotional Response.* In this fourth test procedure, three albino rats and three rhesus monkeys served as subjects. The apparatus for the monkeys was similar to that for the rats except that the dimensions were enlarged to accommodate the larger animal. It consisted of a large metal box with a lever and a grill floor through which an electric shock could be delivered. All subjects were first trained to press the lever for a reinforcement (water for the rats and orange juice for the monkeys), which was delivered on a variable interval schedule (mean = 1 minute). Then, superimposed upon the steady rate of responding generated by this schedule, was a four-minute auditory clicking stimulus which was followed 40% of the time by a shock. The shock was delivered

at the end of the stimulus independently of the lever-pressing behavior. The two and one-half hour-session was composed of a series of clicker periods separated by 12 minutes of the variable interval schedule alone. After extensive training, the clicker interfered with the on-going lever-pressing behavior. The rats tended to remain immobile while the monkeys exhibited considerable agitated disturbance (vigorous jumping, rocking, shaking, defecation, etc.) which was frequently, but not necessarily, accompanied with a decrease in lever-pressing rate. The rate of lever-pressing during the clicker as compared with the rate in the absence of the clicker furnished a quantitative measurement of the emotional effect. A ratio of the two rates provided a useful measure in the rat experiment, but rather large variability, including unexpected high rates during the clicker, reduced the value of the measure in two out of three monkeys. Therefore, direct observation of the monkeys' agitated behavior was added to the battery of measures. Two observers noted the frequency and magnitude of the emotional behavior, and these notes were used in the assessment of drug effects.

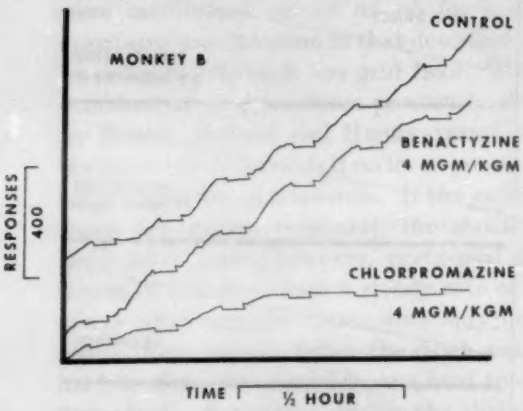


Fig. 4. The effects of benactyzine and chlorpromazine on a conditioned emotional response. The offset of the pen marks the duration of the clicking stimulus which precedes the shock

Benactyzine was administered to the monkeys by stomach tube in doses ranging from 0.5 to 16 mg/kg. The standard time of administration was 30 minutes before the two and one-half hour experimental session, but doses were also tried five minutes before the session. No effect upon the monkeys' agitated disturbance during the clicker was seen after any dose or any time of administration, nor was the lever-pressing rate during the clicker elevated.

In the rat experiments the injections were made intraperitoneally 10 minutes prior to the two and one-half hour session in doses ranging from 0.5 to 12 mg/kg. While changes in rate were observed with benactyzine in the direction of these described in Experiment II, a selective elevation of responding during the clicker was not observed.

Chlorpromazine, with a dose of 4—6 mg/kg, exerted a "quieting" effect upon the monkeys' behavior during the clicker in that the agitated behavior was greatly reduced (i.e., the jumping, rocking, backing, etc.

occurred less frequently, more slowly, and/or less vigorously). This effect was accompanied by a drastically lowered rate of lever-pressing outside the clicker and signs of sedation. The dose range for the above effect was quite narrow. In two monkeys, for example, the effective dose was 4 mg/kg; a dose of 2 mg/kg had little noticeable effect upon the clicker behavior, while 8 mg/kg produced heavy sedation and cessation of almost all behavior. While it was possible to find a dose which reduced the agitation during the clicker without completely eliminating lever-pressing, the "quieting" effect of chlorpromazine was clearly not specific for the pre-shock agitation. Furthermore, in the one monkey whose response rate was disrupted by the clicker, an increase in clicker rate was not produced by the drug, thus confirming the results from the rat experiment. Typical data from this monkey are shown in Fig. 4 and are also representative of the rat data. The main effect shown in this figure is the chlorpromazine-induced decrease in over-all responding. Adiphenine, in doses of 16 mg/kg, was inactive.

## Discussion

The results from the four experiments make it clear that benactyzine has a spectrum of behavioral activity quite different from chlorpromazine. Chlorpromazine had a strong depressant action in all behavior tests used in this study. Benactyzine, on the other hand, appeared to have mixed activity, depending on the dose, the time after administration, and the behavioral test. With low doses and soon after administration, benactyzine showed rate-increasing (stimulant) properties. Evidence for this statement comes from studies of the variable and fixed interval schedules and the early session "warm-up" of avoidance conditioning. While the rate increasing effect is brief and does not always occur, it is nevertheless clear under certain combinations of variables. A similar effect was found in a study of a multiple fixed ratio-fixed interval schedule (Boren and Navarro, 1959). With higher doses benactyzine decreased the terminal rate of responding on fixed interval and the over-all rate on variable interval schedules of reinforcement. That such actions might be due to an overly high dose causing toxicity or a disabling side effect is a likely possibility. Presumably, the avoidance procedure, which involved frequent electric shocks, was less sensitive to these toxic effects than the procedures involving water reinforcement and therefore failed to show the decrease in responding.

In the experiments on the conditioned emotional response, none of the drugs had a beneficial effect upon responding during the pre-shock stimulus. The reduction by chlorpromazine of the visually observed agitation of monkeys occurred only at doses producing heavy sedation. Although it might be said that chlorpromazine has an anti-anxiety or

anti-fear action because of its effects upon avoidance and the pre-shock agitation, it is difficult to rule out the more parsimonious explanation that these effects are due to the general depressant action of chlorpromazine.

Adiphenine, which differs in chemical structure from benactyzine only by a hydroxyl group on the alpha carbon of the diphenylmethane nucleus, caused essentially no changes in behavior at the doses studied. The data are sufficient to show that adiphenine is considerably less potent than benactyzine and that the presence of the hydroxyl group alters the behavioral activity markedly.

## Summary

Adiphenine, benactyzine, and chlorpromazine were studied in four tests of operant behavior: a fixed interval schedule of reinforcement, a variable interval schedule, avoidance conditioning, and a conditioned emotional response. Adiphenine was essentially inactive under all conditions studied. Benactyzine exhibited both rate-increasing and rate-decreasing activity, depending on the dose, the time after administration, and the behavioral test. Chlorpromazine showed a consistent depressant action in all tests, following the usual dose-response relationship.

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# Beruht die experimentelle Katatonie durch Tryptamin auf einer Verdrängung des 5-Hydroxytryptamin?

Von

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In einer Reihe von Arbeiten hat de Jong seit 1920 ausgedehnte Untersuchungen über die Wirkungsweise von Bulbocapnin und verschiedenen anderen Pharmaka an mehreren Tierarten durchgeführt, deren Resultate in seiner Monographie (de Jong u. Baruck 1930) zusammengefaßt sind. Daselbst ist das von ihm beobachtete spezifische Verhalten der Tiere eingehend beschrieben, welches er unter dem Begriff „Experimentelle Katatonie" in die pharmakologische und klinische Literatur einführte. Seither haben sich viele Forscher mit diesem Problem befaßt und dasselbe diskutiert. Der Grund zur Diskussion liegt einerseits darin, daß der klinische Begriff „Katatonie" unscharf umgrenzt war und immer wieder darüber verhandelt wurde, ob die Symptome vom kausal-organischen oder vom psycho-genetischen Standpunkt aus betrachtet werden sollten. Andererseits spielte die Frage der Vergleichbarkeit der klinischen und experimentellen Bilder eine bedeutende Rolle.

Allmählich haben sich die Kliniker davon überzeugt, daß die katatonen Symptome Syndrom-Charakter haben und bei vielen Krankheitsbildern zu erkennen sind. Sie zerfallen in zwei große Gruppen, die man hyperkinetische und hypokinetische Symptome nennt; einige autonome Phänomene ergänzen das Bild. Nach de Jong kann man diese hyper- und hypokinetischen Symptome auch bei Versuchstieren nach Einspritzung eines katatonisierenden Agens beobachten.

Aber in den meisten Fällen treten bei der experimentellen Katatonie die hypokinetischen Phänomene wie Katalepsie, Negativismus und Stupor am stärksten in den Vordergrund und sind deshalb auch am besten studiert worden. Auch wir haben uns hauptsächlich mit diesen hypokinetischen Symptomen beschäftigt und zugleich die autonomen Phänomene genau berücksichtigt. Mit Rücksicht auf die Bedeutung, die man dem 5-Hydroxytryptamin (5-H.T.) hinsichtlich seiner möglichen Funktionen im Zentralnervensystem (ZNS) zuweist, stellten wir Untersuchungen an, welche vielleicht eine tiefere Einsicht in diesen neurohumoralen Mechanismus gestatten.

Die zentral nervöse Wirkung von 5-H.T. wurde von Feldberg und Sherwood (1954) bei Katzen eingehend untersucht, denen die Substanz durch eine Dauerkanüle in den lateralen Gehirnventrikel verabreicht wurde. Nach Dosen von 75—500 $\mu$g 5-H.T. zeigten die Tiere Muskelschwäche, keinen Schlaf oder Duseligkeit, die Augen meist weit geöffnet, Tachypnoea und starken Speichelfluß. Defäkation und Erbrechen wurde nicht beobachtet, Pupillen-Reaktionen werden nicht angegeben. Nur bei höchster Dosierung entstand Tremor der Kopf- und Nackenmuskeln und die Augen wurden geschlossen. Gaddum und Vogt (1956) haben diese Beobachtungen größtenteils bestätigt. Katatone Symptome wurden somit nicht beobachtet bzw. beschrieben.

Die im Jahre 1936 publizierten Ergebnisse von v. Nieuwenhuyzen aus dem Laboratorium von de Jong zeigen, daß er an Katzen mit Tryptamin „Katatonie" erzeugen konnte. Die nahe chemische Verwandtschaft von 5-H.T. und Tryptamin veranlaßte uns, die nachfolgenden Untersuchungen zu unternehmen. Beide Stoffe sind Indol-Derivate; sie unterscheiden sich nur durch eine OH-Gruppe.

Es besteht somit die Möglichkeit, daß Katatonie nach Tryptaminverabreichung durch Verdrängung des 5-H.T. von seinen Receptoren auftritt. Bekannt sind ja die Experimente von Gaddum (1953), welcher nachweisen konnte, daß am isolierten Darm 5-H.T. und Tryptamin an denselben Receptoren eingreifen. Das Verhältnis der Dosen von 5-H.T. zu Tryptamin beträgt 1:30 um einen gleichen Effekt zu erzielen. Für das ZNS ist dieser Antagonismus bisher nicht festgestellt. Sollte jedoch auch im ZNS eine „Konkurrenz-Hemmung" (competitive inhibition) zwischen 5-H.T. und Tryptamin bestehen, so kann man annehmen, daß der Tryptamin-Effekt tatsächlich auf einer Verdrängung des normal anwesenden 5-H.T. beruht, wobei nach der Theorie von Ariëns et al. (1956) und den Ergebnissen von Gaddum (1953) am isolierten Darm Tryptamin eine niedrigere Eigenaktivität (intrinsic activity) im Vergleich zu 5-H.T. haben müßte.

## Methodik

Vor der Wiedergabe der Ergebnisse unserer Untersuchungen soll noch einmal scharf umschrieben werden, was wir unter „Katatonie" verstehen. Denn es hat sich herausgestellt, daß bei der Interpretation der Phänomene leicht Fehler gemacht werden, falls die folgenden Bedingungen nicht streng beachtet werden. Nach unserer Auffassung darf die Diagnose „*Katatonie*" nur dann gestellt werden, wenn nach der Verabreichung des Stoffes die Tiere sowohl Hypokinese, Negativismus wie auch Katalepsie — manchmal in Kombination mit Stupor — aufweisen. Wir fordern ferner, daß nahezu normale motorische Reaktion erfolgt, wenn Schmerzreize u. a. von hinlänglicher Stärke appliziert werden.

Die angewandten Kriterien für die An- bzw. Abwesenheit dieser Phänomene sind folgende:

*Hypokinese.* Bewegungsarmut, Verminderung der motorischen Initiative; Tier geht dann und wann spontan, abwechselnd mit für das betreffende Tier abnormal langen motorischen Ruheperioden. Durchbrechung dieser Perioden tritt auf nach Berühren des Tieres oder nach anderen äußeren Reizen.

*Aktiver Negativismus.* Aktiver Widerstand; Neigung, sich in Ecken zurückzuziehen. Bei Annäherung mit der Hand spontanes Rückwärtsgehen, manchmal kombiniert mit Fauchen.

Abb. 1. Eine katatone Katze

*Passiver Negativismus.* Passiver Widerstand gegen Änderung einer schon eingenommenen Körperstellung. Tier läßt sich wie ein „Block" verschieben; keine Lähmung.

*Katalepsie.* Aktives Festhalten an passiv gegebenen Körperstellungen. Das Tier läßt sich mit nur den Vorder- oder den Hinterpfoten auf einen Holzblock stellen und verharrt in dieser Lage minutenlang; manchmal viel länger. Das Tier läßt sich eine Vorderpfote in den Nacken legen, ohne dieselbe zurückzuziehen (Abb. 1). Auch andere abnormale Stellungen der Extremitäten werden lange Zeit beibehalten.

*Stupor.* Zustand von Unbeweglichkeit mit Verminderung der psychischen Reaktionen. Das Tier ist kataton und döst; es reagiert nicht auf normale äußere Reize.

*Die normale Motorik* prüfen wir mit Applizierung von Schmerzreizen u. a. von hinlänglicher Stärke, worauf das Tier mit nahezu

normaler Abwehrreaktion reagiert wie Ausreißen, Wegspringen, Kratzen usw.; das Tier fällt dann, meistens wieder schnell, in einen katatonen Zustand zurück.

Sofern die Tiere infolge Muskelschwäche über ihre Motorik gar nicht oder nur beschränkt oder in abnormaler Weise verfügen können, notierten wir keine Katatonie, trotz der Tatsache, daß die Tiere stuporös und kataleptisch schienen. Diese Hypotonie gehört nicht zum klinischen Katatoniebild und soll also auch im experimentellen Sinne nicht als „Katatonie" bezeichnet werden.

Die unzulängliche Unterscheidung von Muskelschwäche und Katatonie, wie dies in der Literatur von verschiedenen Autoren gemacht wird, ist unter anderem Ursache für die falsche Deutung der Symptome, die von SACCHI und FAZIO (1957) nach 5-H.T.-Verabreichung beobachtet wurden. Ein weiterer sehr wichtiger Punkt beim Studium der experimentellen Katatonie ist das zu benützende Versuchstier. Die genannte Reihe von Kriterien besagt, daß die motorischen Reaktionen der Tiere gut wahrnehmbar und wiederholbar sein müssen und daß deren Kontrolle richtig stattfindet. Aus diesen Gründen halten wir Ratten und Mäuse für diese Experimente vollkommen ungeeignet. Diese Tiere zeigen nämlich, wenn sie ein wenig zu lange festgehalten werden, oft eine spontane Bewegungsarmut und sogar Katalepsie. Darum eignen sich am besten höhere Tierarten wie Katze, Hund und Affe. Wir haben unsere Versuche mit lebhaften, hantierbaren Katzen von 2—$2^1/_2$ kg Körpergewicht vorgenommen. Für 5-H.T. ist 5-Hydroxy-tryptamin-kreatininsulfat $C_{14}H_{21}O_6N_5S + H_2O$, M.G. 405,4; für Tryptamin ist Tryptamin-hydrochlorid $C_{10}H_{12}N_2 \cdot HCl$, M.G. 197 verwendet worden. Beide Substanzen stammen von der Firma Hoffmann-La Roche.

Um gut vergleichbare Wirkungen beider Amine zu erzielen, wurde die Tryptamin-Dosis der doppelten 5-H.T.-Dosis gleichgestellt. Folgende Versuchsreihen wurden durchgeführt:

A. 5-H.T. oder Tryptamin wurde in wechselnder Dosierung einmalig sub-occipital in die cisterna magna, nach der Methode MÉHES (1938) eingespritzt, um eine zentral-nervöse Wirkung zu sichern. Die Menge der Injektionsflüssigkeit variierte von 0,1—0,2 ml, die Substanzmenge von 5-H.T. und Tryptamin von 0,5—6 mg. Jedesmal wurde nur ein Stoff injiziert. Die Wirkung von 5-H.T. und Tryptamin wurde an denselben Versuchstieren (10 Katzen für jede Dosierung) mit einer Woche Zwischenraum festgehalten (Tabelle 1 und 2).

B. Der kumulative Effekt wurde an sechs Katzen kontrolliert. Drei Katzen erhielten vier Injektionen von 0,5 mg Tryptamin pro Tier, in 0,1 ml, in Abständen von 1 Std sub-occipital injiziert; drei andere Katzen erhielten auf dieselbe Weise vier Injektionen von 1 mg 5-H.T. pro Tier in 0,1 ml (Tabelle 3). Für diese Serieninjektionen wurden die

Katzen jedesmal neu punktiert. Vorversuche mit 0,1—0,2 ml 0,9% NaCl haben gezeigt, daß von geübten Personen die Punktionen mit 1stündiger Pause bei derselben Katze wenigstens 6mal ohne Schaden wiederholbar sind.

C. Die gegenseitige Beeinflussung der Wirkungen von 5-H.T. und Tryptamin wurde auch nach sub-occipitaler Injektion an sechs Katzen untersucht. Den Tieren wurde erst 1,5—2 mg Tryptamin und 1 Std später 3—6 mg 5-H.T. verabreicht (Tabelle 4). Andere sechs Katzen erhielten zuerst 2—3 mg 5-H.T. und 1 Std später 1,5—4 mg Tryptamin (Tabelle 5).

D. Die Untersuchung der Konkurrenzwirkung von 5-H.T. und Tryptamin wurde nach Vorbehandlung mit Iproniazid[1] (Marsilid), 100 mg/kg subcutan vorgenommen. Iproniazid wurde 16 Std vorher verabreicht und dann an sechs Katzen zuerst 10 mg/kg Tryptamin und 1 Std später 20 mg/kg 5-H.T. subcutan injiziert. Ebenso wurde die Konkurrenzwirkung beider Substanzen, in umgekehrter Reihenfolge verabreicht, nach Iproniazid-Vorbehandlung untersucht.

## Ergebnisse

Die Resultate der unter A.—C. erwähnten Versuchsanordnungen sind in den Tabelle 1—5 dargestellt.

Tabelle 1. *Katzen. Einspritzung von 5-H.T. sub-occipital*

| 5-H.T. pro Katze mg | Speichelfluß | Pupillenverengerung | Defäkation | Erbrechen | Atmung | katatone Phänomene | Muskelschwäche | Erholung der autonomen Phänomene nach: |
|---|---|---|---|---|---|---|---|---|
| 0,5 | + | + | – | – | + | – | – | $^1/_2$ Std |
| 1 | + | + | – | – | + | – | – | $^1/_2$ Std |
| 1,5 | ++ | ++ | + | – | + | – | – | $^1/_2$ Std |
| 2 | ++ | +++ | ++ | + | ++ | – | + | 1 Std |
| 3 | ++ | +++ | +++ | + | +++ | – | + | $1^1/_2$ Std |
| 6 | ++ | +++ | +++ | + | +++ | – | +++[1] | 3 Std |

[1] Nach einer kurzen Periode tonischer Krämpfe und Tremor der Kopf- und Extremitätenmuskulatur.

Definierung der Parameter der Tabellen 1 und 2. *Speichelfluß:* — kein Speichelfluß, + dann und wann ein Tropfen, ++ Speichelfaden fließt aus dem Maul, +++ starker ständiger Speichelfluß; *Pupillenverengerung:* — keine Verengerung, + mäßige Verengerung, ++ starke Verengerung, +++ Pupillen nur noch schlitzförmig; *Defäkation:* — keine Defäkation, + 1- oder 2mal Defäkation mit normalen Faeces, ++ mehrmals Defäkation mit weichen Faeces, +++ häufige Defäkation mit schleimigen Faeces; *Erbrechen:* — kein Erbrechen, + 1- oder 2mal Erbrechen;

[1] Die Substanz wurde uns in dankenswerter Weise von der Firma Hoffmann-La Roche, Basel, zur Verfügung gestellt.

Tabelle 2. *Katzen. Einspritzung von Tryptamin sub-occipital*

| Tryptamin pro Katze mg | Speichelfluß | Pupillenverengerung | Defäkation | Erbrechen | Atmung beschleunigt | katatone Phänomene | Muskelschwäche | Erholung der autonomen Phänomene nach: | Erholung der katatonen Phänomene nach: |
|---|---|---|---|---|---|---|---|---|---|
| 0,5 | + | – | – | – | – | – | – | 20—30 min | + |
| 1 | + | – | – | – | – | + | – | ½—2 Std | ½ Std |
| 1,5 | + | + | – | – | – | ++ | – | 2—6 Std | 2 Std—2 Tg. |
| 2 | + | + | – | – | – | ++ | – | 5—12 Std | 5 Std—2 Tg. |
| 3 | + | ++ | – | – | + | +++ | – | 1—4 Tg. | 1—4 Tg. |
| 6 | + | +++ | ++ | + | +++[1] | | | | |

[1] Epileptiforme Krämpfe, alle Tiere sterben innerhalb der 1. Std.

*Atmung:* — normale Atmungsfrequenz, + mäßige Beschleunigung, ++ sehr starke Beschleunigung, +++ sehr starke Beschleunigung mit offenem Maul und Keuchen; *katatone Symptome*: — keine, + Hypokinese und Negativismus, ++ Katalepsie mit leichtem Stupor, +++ Katatonie, stuporös; *Muskelschwäche:* — keine, + leichte, +++ Tier liegt völlig entspannt auf dem Boden.

Für die Versuche der Tabellen 1 und 2 wurden für jede der sechs Dosierungen von Tryptamin und 5-H.T. mindestens 10 Katzen verwendet. Die wiedergegebenen Resultate stellen somit gewissermaßen Mittelwerte dar. Vergleicht man die Wirkungen der einmaligen intracisternalen Verabreichung beider Substanzen miteinander, so kann man aus den Tabellen 1 und 2 folgendes schließen:

1. Beide Substanzen verursachen einen parasympathischen Symptomen-Komplex, wobei aber bei gleicher Mol-Dosierung der 5-H.T.-Effekt viel kräftiger ist als der nach Tryptamin.

2. Tryptamin ist imstande, eine Katatonie zu erzeugen mit einer von der Dosierung bedingten Dauer; 5-H.T. erzeugt niemals eine Katatonie, in höheren Dosierungen aber Muskelschwäche.

3. Der Zeitraum zwischen der Verabreichung und völliger Erholung des Tieres ist nach 5-H.T. viel kürzer als nach Tryptamin.

Die Ursache der längeren Dauer der Wirkung des Tryptamins könnte möglicherweise die Folge einer langsameren Entgiftung dieses Amins sein. Wenn das zutrifft, dann sollte für Tryptamin ein kumulativer Effekt nachweisbar sein, nicht aber für 5-H.T., oder dann nur in geringerem Ausmaße.

Zur Abklärung dieser Frage diente die Versuchsanordnung B., deren Resultate in der Tabelle 3 zusammengefaßt sind.

Daraus geht hervor, daß nach Tryptamin ein kumulativer Effekt erreicht wird, nicht aber nach 5-H.T. Die Differenz in der Dauer des Symptomen-Komplexes nach 5-H.T. und Tryptamin-Darreichung kann deshalb der größeren Beständigkeit des Tryptamins zugeschrieben werden.

Tabelle 3

| Injektion Nr. | 4malige sub-occipitale Injektion von Tryptamin 0,5 mg/Tier/Std in 0,1 ml | | | 4malige sub-occipitale Injektion von 5-H.T. 1 mg/Tier/Std in 0,1 ml | | |
|---|---|---|---|---|---|---|
| | Symptome | | | Symptome | | |
| | Katze 1 | Katze 2 | Katze 3 | Katze 4 | Katze 5 | Katze 6 |
| 1 | Keine Katatonie, keine autonomen Symptome | Keine Katatonie, keine autonomen Symptome | Keine Katatonie, keine autonomen Symptome | Speichelfluß, schnelle Atmung, keine Katatonie, keine Muskelschwäche; nach $^1/_2$ Std wieder normal | Symptome wie bei Katze 4 | Symptome wie bei Katze 4 |
| 2 | Speichelfluß, keine Katatonie | Speichelfluß, keine Katatonie | Speichelfluß, keine Katatonie | Gleich wie nach der ersten Injektion | Symptome wie bei Katze 4 | Symptome wie bei Katze 4 |
| 3 | Speichelfluß, Pupillenverengung, Katatonie 3 Tage dauernd | Speichelfluß, keine Katatonie | Speichelfluß, keine Katatonie | Gleiche Symptome wie oben, enge Pupillen, Defäkation, keine Katatonie, keine Muskelschwäche. Nach $^3/_4$ Std wieder normal | Symptome wie bei Katze 4 | Symptome wie bei Katze 4 |
| 4 | — | Speichelfluß, Pupillenverengung, Katatonie 24 Std dauernd | Speichelfluß, Pupillenverengung, Katatonie 2 Tage dauernd | Nur Speichelfluß, keine Katatonie, keine Muskelschwäche | Symptome wie bei Katze 4 | Symptome wie bei Katze 4 |

Nach der Ermittlung der differenten Wirkung beider Substanzen wurde entsprechend der Versuchsanordnung C. die gegenseitige Beeinflussung der Wirkungen beider Stoffe untersucht. Die Ergebnisse dieser Versuchsreihe sind in der Tabelle 4 wiedergegeben.

Diese Resultate lassen erkennen, daß die von Tryptamin regelmäßig ausgelöste Katatonie durch 5-H.T. mindestens nach 30 min aufgehoben wird, während die Tryptamin-Katatonie normal, nach denselben Dosen von 1,5 und 2 mg, stunden-, ja tagelang anhält.

Tabelle 4

| | $9^{00}$ Uhr | $9^{10}$ Uhr | $10^{00}$ Uhr | $10^{15}$ Uhr | $10^{30}$ Uhr |
|---|---|---|---|---|---|
| Katze 1 und Katze 2 | 1,5 mg Tryptamin in 0,15 ml | Speichelfluß, enge Pupillen, *Katatonie* | 3 mg 5-H.T. in 0,1 ml | Speichelfluß, schnelle Atmung, enge Pupillen, *Katatonie* | Speichelfluß, schnelle Atmung, enge Pupillen, Muskelschwäche, *keine Katatonie* |
| Katze 3 und Katze 4 | 2 mg Tryptamin in 0,2 ml | Speichelfluß, enge Pupillen, *Katatonie* | 4 mg 5-H.T. in 0,15 ml | Speichelfluß, schnelle Atmung, Defäkation, Erbrechen, *Katatonie* | Speichelfluß, schnelle Atmung, enge Pupillen, Muskelschwäche *keine Katatonie* |
| Katze 5 und Katze 6 | 2 mg Tryptamin in 0,2 ml | Speichelfluß, enge Pupillen, *Katatonie* | 6 mg 5-H.T. in 0,2 ml | Speichelfluß, schnelle Atmung, enge Pupillen, *keine Katatonie*, Tremor abwechselnd mit Muskelschwäche | Speichelfluß, enge Pupillen, *keine Katatonie*, Tremor abwechselnd mit Muskelschwäche |

Die Versuchsreihe, wobei erst 5-H.T. und 1 Std später Tryptamin beide sub-occipital, injiziert wurden, ist in der Tabelle 5 zusammengestellt.

Aus diesen Resultaten kann man folgende Schlüsse ziehen:

1. 5-H.T., vorher verabreicht, ist imstande, die Katatonieentwicklung durch Tryptamin, welche normalerweise nach 10 min eintritt, um etwa 1 Std aufzuschieben.

2. Das Verhältnis zwischen den respektiven Dosen von 5-H.T. und Tryptamin bedingt den Zeitpunkt des Auftretens der Katatonie, was bei einer Konkurrenz-Hemmung zu erwarten ist.

Daß die durch Tryptamin erzeugte Katatonie durch die vorangegangene 5-H.T.-Injektion nicht ganz verhütet, sondern nur aufgeschoben wird, ist durch die oben beschriebene längere Wirkungsdauer des Tryptamins gut zu verstehen.

Weiteren Aufschluß über die Konkurrenz-Wirkung von Tryptamin und 5-H.T. war durch eine Vorbehandlung der Tiere mit Iproniazid zu erwarten, weil dadurch die Differenzen der Beständigkeit der beiden Substanzen aufgehoben waren. Alle Substanzen wurden in diesen Versuchen subcutan injiziert. In Vorversuchen ergab sich, daß unter dem Einfluß von Iproniazid (100 mg/kg) schon 10 mg/kg Tryptamin nach einigen Minuten Katatonie erzeugten, welche 4 Std dauerte, wäh-

Tabelle 4

| 11⁰⁰ Uhr | 12⁰⁰ Uhr | 13⁰⁰ Uhr | Erholungszeit der katatonen Symptome nach der 5-H.T.-Injektion | Erholungszeit der katatonen Symptome nach nur Tryptamin-Injektion (Tabelle 2) |
|---|---|---|---|---|
| Völlige Erholung | — | — | 30 min | 2 Std bis 2 Tagen |
| Schnelle Atmung, Muskelschwäche, *keine Katatonie* | Völlige Erholung | — | 30 min | 5 Std bis 2 Tagen |
| Speichelfluß, schnelle Atmung, enge Pupillen, *keine Katatonie*, kein Tremor, keine Muskelschwäche | Speichelfluß, schnelle Atmung, enge Pupillen, *keine Katatonie* | Völlige Erholung | 15 min | 5 Std bis 2 Tagen |

rend 10—20 mg/kg 5-H.T. absolut keine Katatonie verursachten (VAN ANDEL 1958). Die Konkurrenz-Wirkung wurde dann 2mal an je drei Katzen nach Vorbehandlung mit Iproniazid untersucht. 16 Std nach 100 mg/kg Iproniazid erhielten drei Katzen je 10 mg/kg Tryptamin und 1 Std später 20 mg/kg 5-H.T. Die Tiere zeigten zuerst Speichelfluß und Pupillenverengerung und 5 min später Katatonie; die nachfolgende 5-H.T.-Injektion war imstande, die Katatonie innerhalb $^1/_2$ Std zu eliminieren. Drei anderen Tieren wurde nach Iproniazid-Vorbehandlung 20 mg/kg 5-H.T. injiziert, sie wiesen nach 5 min Speichelfluß, enge Pupillen, Defäkation und schnelle Atmung auf. 1 Std später erfolgte die subcutane Injektion von 10 mg/kg Tryptamin; es trat in keinem Falle Katatonie auf.

Das wichtigste Resultat dieser Versuche ist, daß unter Einfluß von Iproniazid durch eine vorangegangene 5-H.T.-Injektion das Entstehen einer Tryptamin-Katatonie dauernd verhütet werden konnte, während der Versuch, in umgekehrter Folge der beiden Substanzen, wie üblich verlief, d. h., 5-H.T. vermochte die durch Tryptamin erzeugte Katatonie aufzuheben.

Alle Resultate zusammen erlauben die Hypothese, daß beide Substanzen auch im Z. N. S. auf die gleichen Rezeptoren angreifen, daß dabei die Eigenaktivität (intrinsic activity) von Tryptamin kleiner ist als die von 5-H.T., und deshalb Tryptamin ein Konkurrenz-Hemmer

Tabelle 5

| | 9⁰⁰ Uhr | 9¹⁵ Uhr | 10⁰⁰ Uhr | 10¹⁵—10³⁰ Uhr | 11³⁰ Uhr | 11⁴⁵ Uhr | 12⁴⁵ Uhr | 13⁴⁵ Uhr |
|---|---|---|---|---|---|---|---|---|
| Katze 1 und Katze 2 | 3 mg 5-H.T. in 0,3 ml | Übliche autonome 5-H.T.-Symptome | 1,5 mg Tryptamin in 0,15 ml | Übliche autonome 5-H.T.-Symptome keine Katatonie | Autonome 5-H.T.-Symptome aufgehoben; keine Katatonie | Keine Katatonie | Katze 1 *Katatonie*, Katze 2 keine Katatonie | Keine Katatonie, völlig normal |
| Katze 3 und Katze 4 | 3 mg 5-H.T. in 0,3 ml | Übliche autonome 5-H.T.-Symptome | 2 mg Tryptamin in 0,2 ml | Übliche autonome 5-H.T.-Symptome keine Katatonie | Autonome 5-H.T.-Symptome aufgehoben; keine Katatonie | *Katatonie* | *Katatonie* | *Katatonie* |
| Katze 5 und Katze 6 | 2 mg 5-H.T. in 0,2 ml | Übliche autonome 5-H.T.-Symptome | 4 mg Tryptamin in 0,2 ml | Autonome 5-H.T.-Symptome aufgehoben. Tonische Konvulsionen, nachher *Katatonie* | *Katatonie*, keine Konvulsionen | *Katatonie* | *Katatonie* | *Katatonie* |

(competitive inhibitor) von 5-H.T. sein muß. Die Tryptamin-Katatonie wäre dann möglicherweise aufzufassen als die Folge eines Fehlens von 5-H.T. an bestimmten Rezeptoren im Z.N.S.


## Summary

Tryptamine applied intracisternally can produce catatonia in cats. This effect can be antagonized by 5-H.T. which itself never causes catatonia.

The central-autonomic effects elicited by injections of 5-H.T. and of Tryptamine in the cisterna magna are qualitatively the same; Tryptamine having the weaker effect.

These facts lead us to the hypothesis that both substances act in the C.N.S. on the same receptors, Tryptamine having the lower intrinsic activity; thus, Tryptamine must be a competitive inhibitor of 5-H.T. The catatonia produced by Tryptamine might then be regarded as the consequence of a shortage of 5-H.T. on certain receptors in the C.N.S.

The effect of Tryptamine lasts longer than that of 5-H.T.; Tryptamine also shows a cumulative pattern, 5-H.T. does not. After Iproniazid (Marsilid) administration this difference is not observed, being obviously dependent on the rate of de struction.

Without Iproniazid, 5-H.T. can suppress or prevent the Tryptamine-catatonia only for a restricted period of time, with Iproniazid this suppression respectively prevention is unlimited.

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# An Investigation of Some Therapeutic and Physiological Effects of Perphenazine in Huntington's Chorea

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With 1 Figure in the Text

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Hyoscine and also arsenic in large doses were long considered to be effective in Huntington's Chorea (Sinkler 1889) and similarly hyoscyamine, atropine and scopolamine combined in a proprietary preparation (Rabellon) were favourably described in recent years by Tomlinson (1947). Interest in possible drug therapies for this condition appears to have increased however since the paper of Goldman (1952) in which the use of procaine amide was recommended, although subsequent investigations, reviewed by Merskey (1958) gave only limited support to Goldman's claim. Reserpine, which was first used by Chandler (1955), has been accepted as effective by a number of authors (Lazarte et al. 1955; Brander 1956; Kempinsky et al. 1960) who often used cinematographic techniques to verify their conclusions. But a high incidence of undesirable side-effects has typically been found in such studies with reserpine. For current treatment the choice appeared to Pakenham-Walsh (1960) to lie between thiopropazate recommended by Matthews (1958) and perphenazine, described for one case by Laricchia and Baseri (1958). In addition the thorough study of Mertens and Fischer (1958) showed clear clinical benefit in choreic states from the use of both intravenous and oral perphenazine. We therefore decided to attempt an assessment of the effects of perphenazine in four cases.

## Methods

The trial was originally designed according to a double-blind pattern, the key to the placebo and drug being kept by the Hospital Pharmacist. In the event the emergence of side-effects with substance "A" made us confident that the trial was no longer "blind" and we therefore confined our observations to the state of the patients before, during and after the oral administration of this drug which we believed, correctly as it turned out, to be perphenazine. The dose of the drug was varied in the individual cases so as to obtain the maximum level which appeared beneficial without causing side-effects. This ranged from 8 mgms t.d.s.

to 24 mgms t.d.s. The observations made during the treatment period for comparison with the pre- and post-treatment periods were recorded in the fourth week of administration of the drug at this apparently optimum level. The dose was then gradually reduced over a few days and final post-treatment assessments were made in the fourth week after the last dose had been taken. The period of the trial was September—December 1960.

Observations were made in all cases of the subjective response, nursing needs, physical activity and habits and the involuntary movements and state of the musculature. In one patient (Case 1) this was all that was possible by reason of her deteriorated state. In the remaining three patients (Cases 2, 3 and 4 below) records of written performance were obtained in conjunction with the clinical observations. Further in these three patients performance was timed on a block-sorting test of manual dexterity described previously (MERSKEY 1958) and finger-movement was recorded. The apparatus for the block-sorting test consists of a wooden tray with three compartments. Twenty red and twenty white blocks are placed in the central compartment. The outer compartments are red and white respectively and the subject is instructed to sort the blocks as quickly as possible into the compartment of their own colour. Timing was done with a stop-watch. The apparatus for recording finger movement consists of a lever resting upon an enclosed piezo-electric crystal from a microphone insert; the potential change across the crystal caused by varying pressures was fed into the input of one channel of an Ediswan E.E.G. instrument thus giving a pen write-out related to changes in finger-pressure. To our knowledge the suggestion for its use was first made by MALMO and SHAGASS (1949). Lastly in the case of three patients (Cases 1, 3 and 4) who appeared to be showing some change as a result of the perphenazine brief cinematographic records of their movements were obtained in the fourth weeks of the treatment and post-treatment periods.

## Case histories and results

### *A. Clinical*

**Case 1.** M. V. Female, 56 years, married. Her son of 28 years was recently a patient in Cherry Knowle Hospital with a Paranoid Schizophrenic illness. No other family history was available to suggest hereditary chorea. She was admitted to Cherry Knowle Hospital in 1959 but her illness was manifest four years previously. On admission her general condition was poor. She was able to walk unaided and dress herself but had to be fed. She was emotionally labile, weeping profusely or aggressive without cause. Before treatment she looked senile, was doubly incontinent, confined to her chair and had to be carried to bed.

She was demented, incoherent in speech, and would often weep profusely when spoken to. Generalised involuntary movements of all parts of body were present varying between 50—60/minute; her tongue kept protruding from her mouth at an uncountable rate.

She was started on perphenazine 8 mgm t.d.s. which was gradually increased to 24 mgm t.d.s. and after two weeks of this there was a marked change. She fed herself for the first time since admission and managed to walk with the minimum of support; her involuntary movements had lessened somewhat.

Three weeks after commencing treatment with perphenazine there was a sudden rapid deterioration in her physical condition. She became drowsy and she developed features of Parkinsonism. Her head slumped forward and her chin fixed on her chest making feeding almost impossible. She developed a mild pyrexia probably due to infected pressure sores. Penicillin therapy was commenced and benzhexol (Artane) 2 mgm t.d.s., and although the blood count showed no agranulocytosis the perphenazine was discontinued because of the above reaction.

Within one week her pyrexia had subsided and the features of Parkinsonism cleared, the nursing staff were able to feed her and it was decided after two weeks that it would probably be worth trying her once more with perphenazine. She was started on 8 mgm t.d.s. and after two weeks this was increased to 16 mgm t.d.s. and she continued on this dose for a further two weeks.

During this period of treatment there was again a remarkable change in her involuntary movements which almost entirely disappeared and her tongue was no longer protruded from her mouth. She continued to eat well although she required to be fed and she was unable to walk. She showed no emotional lability and was cheerful and contented.

Within a few days of stopping perphenazine there was a return of her involuntary movements; these varied between 10—15/minute during the four weeks after stopping the perphenazine. During this period the involuntary movements were never as marked as they were prior to starting perphenazine.

*Opinion.* Considerable clinical improvement in this case.

**Case 2. G. A. H. Male, 46 years, separated. His mother died in Cherry Knowle Hospital with chorea and dementia. He had been deaf for many years (secondary to old bilateral otitis media) and prone to temper tantrums all his life. He was admitted to Cherry Knowle Hospital 1957 with a history of bad temper and aggressive behaviour towards his wife.**

**Before treatment he was fatuous, euphoric and quite devoid of insight. His performance in simple arithmetic and serial sevens was excellent. His speech was explosive and slurred but coherent; involun-**

tary movements in each upper limb were present at a rate of 3 to 4 per minute; his gait was slightly unsteady and on a wide base; performance in the finger-nose test was excellent.

Treatment commenced with 8 mgm perphenazine t.d.s. and after 3 days was increased to 16 mgm t.d.s. After one day on this dose he complained of being dizzy, unsteady on his feet and unable to play snooker. Clinical examination showed no reason for this but it was decided for the rest of the trial to restrict his dosage of perphenazine to 8 mgm t.d.s. on the assumption that the symptoms were hypotensive, although his blood pressure in the recumbent position was not changed.

During the trial period there was no apparent motor change; his movements remained at the rate of 3 to 4/minute in each upper limb. The nursing staff reported, however, that he was much more placid and co-operative and had had no aggressive outburst since he commenced perphenazine.

Although there was no evidence of improvement during the treatment, subjectively he was pleased saying "The tablets help me to walk farther and easier".

Post-treatment assessment four weeks after the last dose had been taken showed no obvious clinical improvement. There was throughout no variation in the written tests.

*Opinion.* No definite evidence of improvement.

**Case 3.** F. P. Male, 49 years, married. Brother previously a patient in Cherry Knowle Hospital with chorea and dementia.

First admitted here 1959 with a history of violence towards his wife, he left hospital 2 weeks later against medical advice, but was readmitted one year later with a similar history. Signs of illness were manifest in 1958 when he lost his job as a labourer for being inefficient. His work-mates at the time had started to call him "rock and roll".

Before treatment, memory and orientation were good but on being asked to take seven from 100, he answered "30". His speech was slurred and at times incoherent. Involuntary movements were present in each upper limb at the rate of 15—21/minute. In the finger to nose test he was jerky but accurate; his gait was unsteady and on a wide base, and he was unable to walk heel to toe.

The nursing staff observed that he was slovenly in appearance but ate well without spilling his food.

He was started on 8 mgm Perphenazine t.d.s. and this was gradually increased to 32 mgm t.d.s. However with that dose he became drowsy, dull and apathetic and looked extremely depressed, necessitating a reduction to 24 mgm t.d.s. He was held on this dose during the remainder of the trial.

During treatment with perphenazine there was no apparent change in the rate of involuntary movements although his ability to join two marked points showed some improvement. When questioned he stated "The tablets are helping me, they're helping my finger movements".

Within a few days of discontinuing perphenazine his movements increased to a rate of between 50—60/minute, and also in amplitude and vigour. Further with the written test his performance appeared to deteriorate after stopping treatment.

*Opinion.* No real clinical improvement during treatment but definite deterioration after perphenazine stopped.

**Case 4.** D. M. Male, 46 years, single. Mother died with choreo-athetosis and dementia. Admitted to Cherry Knowle Hospital in 1958 with complaint of "falling about". He stated he had been getting less steady on his feet during the previous 10 years.

He was a fatuous cheerful co-operative man unable to give much account of himself who gave his age incorrectly as 44 and the year as 1962. Asked to take 7 from 100 he replied "I'm no good at that". His speech was slurred but coherent, there was generalised mild choreiform movement at the rate of 20—30/minute; his tongue was unsteady and moved in and out of his mouth; his grip would wax and wane. In moving his finger to his nose he was unsteady but accurate. His gait was unsteady, he walked on a wide base and he could not walk heel to toe.

The nursing staff reported no change since admission and he ate well without spilling food; he was clean but untidy.

He was started on 8 mgm perphenazine t.d.s. and this was gradually increased over a period of 3 weeks to 32 mgm t.d.s. but after 4 days on this dosage, he became very drowsy necessitating reduction to 24 mgm t.d.s. which was continued for the rest of the trial period. During treatment with perphenazine there was no evidence clinically of improvement or deterioration. His involuntary movements remained at the rate of 20—30 per minute.

He observed "I think I'm better without the tablets they weren't doing me any good". The nursing staff reported no apparent change and the written test showed no variation.

*Opinion.* No evidence of improvement.

Thus one patient (Case 1) showed undoubted clinical improvement with the drug whilst another showed only side effects. The other two patients showed no convincing clinical benefit but one of them was apparently worse at least for a short period after stopping the drug, a phenomenon which was previously noted in two cases with procaine amide (Merskey 1958).

*B. Test measurements and finger-movement records*

The results with the block sorting test are set out in Table 1. The mean figures shown represent the averages of twelve trials for each patient in each period. It will be seen that there is a significant improvement in the treatment period in Case 2: since this improvement is largely maintained in the post-treatment period it must be discounted as a possible practice effect. The other two patients were very significantly less dexterous when under the influence of perphenazine.

Table 1. *Mean scores in seconds of twelve trials in each period on block-sorting test of manual dexterity*

| Patient Case | Before treatment sec | During treatment sec | After treatment sec | Significance of differences between treatment and pre-treatment periods | Significance of differences between treatment and post-treatment periods |
|---|---|---|---|---|---|
| 2 | 24.0 | 21.7 | 22.0 | $P<0.05$ | N.S. |
| 3 | 46,8 | 56.0 | 43.5 | $P<0.01$ | $P<0.01$ |
| 4 | 47.6 | 55.7 | 45.5 | $P<0.01$ | $P<0.01$ |

The results of the finger-movement recording are illustrated in the figure. Within each record there was a good deal of spontaneous fluctuation. The most extreme examples of this are shown first (A′ and A). To meet this circumstance a fixed scheme of measurement was used.

Table 2. *Average scores of random samples of finger-movement deflections; each average is based on 45 measured deflections*

| Patient Case | Before treatment mm | During treatment mm | After treatment mm | Significance of differences between treatment and pre-treatment periods | Significance of differences between treatment and post-treatment periods |
|---|---|---|---|---|---|
| 2 | 7.9 | 4.7 | 7.5 | $P<0.01$ | $P<0.01$ |
| 3 | 9.6 | 6.9 | 11.6 | $P<0.01$ | $P<0.001$ |
| 4 | 15.4 | 9.8 | 12.7 | $P<0.001$ | $P<0.02$ |

Three records were taken from each patient in each period, and each record was sampled at pre-determined intervals for the 3 largest deviations in each of five sections. The mean results of the measurements are set out in Table 2 and indicate that all 3 patients showed a highly significant reduction of random finger-movements in the treatment period. This trend towards less random deviation with treatment is apparent also on visual inspection of the records and is illustrated for one case in the figure by samples of the records before, during and after treatment. ($B_1$, $B_2$ and $B_3$ respectively.)

*C. Cinematography*

The cinematographic records showed a difference in the case of each of the three patients photographed in the direction of increased involuntary movements and jerkiness during the post-treatment as compared with the treatment period. In Case 1 this was very marked and in Cases 3 and 4 it was less marked but still definite. It was least in Case 3.

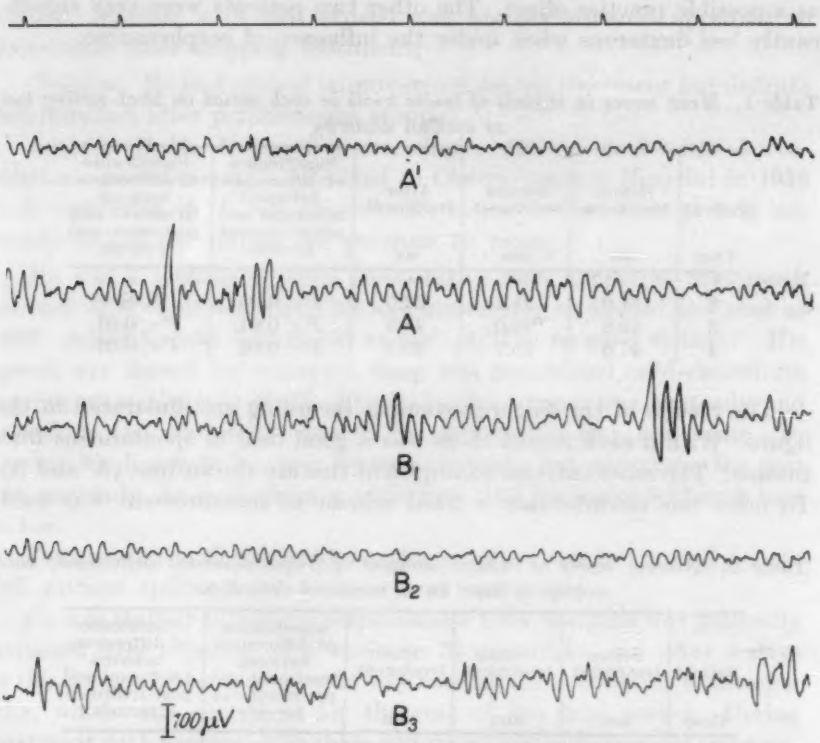


Fig. 1. Finger Movement Records. A and A'. Selected samples from one record to show degree of random fluctuation which may occur. $B_1$, $B_2$ and $B_3$. Representative samples from the records of one patient before ($B_1$), during ($B_2$) and after ($B_3$) treatment

## Discussion

Although the clinical findings of benefit were definite in only one case the results of the finger-movement records and cinematography support the view that perphenazine is in fact capable of reducing the range and frequency of the involuntary movements and improving the gait and motor abilities in chronic chorea. It did this in all 4 cases studied here, even when improvement as judged clinically was not necessarily apparent. At the same time the actual speed in a motor task of two of these patients was reduced. To this extent it may appear

that perphenazine acts by producing either a Parkinsonian effect with muscular rigidity or psychomotor retardation. Although the finger movement records and clinical observations and cinematography did not indicate the presence of any noteworthy Parkinsonian signs in Cases 2, 3 and 4 during treatment, it must be recognised that a reduction in involuntary movements may be seen at times in the more advanced stages of HUNTINGTON'S Chorea when the extending degenerative process produces Parkinsonian features (BELL 1934) including rigidity. Sometimes in our own observations in other subjects there is a typical mask-like facies and like DENNY-BROWN (1960a) we have noticed the appearance of rigidity with slower and more characteristically athetotic movements in the advanced stages of HUNTINGTON'S Chorea. In such cases the persisting involuntary movements may be less frequent, slower and of less amplitude, but they are nevertheless perfectly definite and indeed more readily observed in detail. They appear to be modified by the prevailing increase in muscular tone and it is possible that a minor degree of this phenomenon is responsible for our findings of a concomitant reduction in motor speed and involuntary movements. Such a slowing of the involuntary athetotic movements or of tremor in the presence, and apparently as a consequence, of rigidity is recognised by DENNY-BROWN (1960a) in such an instance amongst others as double athetosis and could certainly be adduced as an explanation of the findings in our first case.

On the other hand the facts we have found are simply that the involuntary movements are reduced as the patient becomes slower. This may be considered to be a narcotic effect of the drug in line with the tendency of sleep or barbiturate sedation to abolish extra-pyramidal signs. But the lack of noteworthy somnolence in our patients at effective treatment levels is against such a hypothesis.

A third viewpoint is that of KEMPINSKY et al. (1960) who attributed the improvement in their cases treated with reserpine to the overall reduction of "psychomotility" to which they held choreic movement to be related. Such a concept of psychomotility may be relevant in so far as excitement and emotional states affect choreic movement but does not take into account the importance of postural mechanism and the flow of movement to which again DENNY-BROWN (1960a and b) has drawn attention. Since the most marked abolition of movement occurred in our Case 1 at the time when she showed the most definite signs of rigidity we incline rather to the view that the possible benefits of phenothiazine drugs in chorea in some cases are closely related to their power to impose muscular rigidity.

In other instances there may be a different mechanism since MERTENS and FISCHER (1958) using electromyographic control were able to show

that Parkinsonian rigidity and tremor were both removed in one patient shortly after an intravenous injection of perphenazine, and it has in fact been found with procaine amide in HUNTINGTON'S Chorea that clinical improvement and some increase in motor speed may occur together (MERSKEY 1958). Clinical rigidity need not therefore be produced in all cases with extra-pyramidal signs that are to benefit from perphenazine or other centrally active compounds although it is probably one factor of importance at times. Whatever the exact mechanism we think that perphenazine and similar compounds probably have a differential neuroplegic or neuroregulatory effect which is of value in individual cases of choreoathetotic states. In our 4 subjects it was considered to be of sufficient clinical value to be restored only in one when the trial was completed and this is but another indication of the fact that even if a substance is pharmacologically active the question as to whether its use is worthwhile has to be decided by clinical judgement.

## Summary

The results are reported of an investigation of the effects of perphenazine on 4 patients with HUNTINGTON'S Chorea. Data were obtained from clinical observations, performance in objective tests, finger-movement recording and cinematography. One patient showed evident clinical benefit and this was confirmed in her case as well as demonstrated in 2 more by the cinematograph film. Three of the 4 in whom it was possible to record finger-movement showed significant reduction of involuntary movements recorded by a piezo-electric system. Two of these last three however were significantly slower in a timed test of manual dexterity. The theoretical import of these findings is discussed and it is concluded that perphenazine will certainly reduce the amplitude of involuntary movement in chorea, and that this may sometimes be due to the concomitant imposition of muscular rigidity, but that a differential neuroplegic or neuroregulatory action is likely to occur as well.

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# Comparison of the Effect of Thioridazine and Chlorpromazine on Chronic Schizophrenic Psychosis Using Double Blind Technique

By

B. BORUP SVENDSEN, A. FAURBYE and P. KRISTJANSEN

*(Received March 17, 1961)*

## The purpose of the investigation

The authors wished to ascertain whether thioridazine has a better therapeutical effect or fewer side-effects than chlorpromazine in the treatment of chronic schizophrenics. Thioridazine (Melleril) is 3-methyl-mercapto-10 (2-(N-methyl-piperidyl-(2″))-ethyl-(1′)) phenothiazine.

A preliminary investigation (KRISTJANSEN and BORUP SVENDSEN) indicated that further study of the preparation was warranted.

## Methods

**The Patients.** The basic material of this investigation consisted of 61 patients—28 males and 33 females, who had all been hospitalized for many years with schizophrenia and who had practically all previously had the most intensive treatment (the hospital having to a great extent used electric convulsive therapy, insulin coma, leucotomy, chlorpromazine, and reserpine).

The average age of the males was 52 and of the females 53.

Table 1. *Patients entering study. All hospitalized for many years in Sct. Hans Mental Hospital*

| Diagnosis | M | F | Total |
|---|---|---|---|
| Schizophrenia | 28 | 33 | 61 |
| Years since 1. admission to psychiatric institution, in average | 20,5 | 25,5 | 23 |
| Range in years | 4—40 | 9—47 | 4—47 |
| Number of patients receiving other treatment | 0 | 0 | 0 |

**The program of the investigation.** The authors preferred a direct comparison of chlorpromazine—with which drug they felt well experienced and the efficiency of which towards schizophrenia they consider established—with thioridazine to the use of placebo-technique, as the results from the former procedure were expected to be easier to interpret.

Each patient passed through a preliminary period of 3 weeks, a first treatment period of 12 weeks and a second treatment period of 16 weeks,

the final 12 of which were to be compared to the first treatment period. During the preliminary period the patients had no medicine—to avoid overlapping of pharmacological effect from preceding treatment—during the first treatment period either thioridazine or chlorpromazine, and vice versa during treatment period number two.

The observers were aware of the fact that no treatment was given in the first three weeks. During this period some of these very ill patients developed classical symptoms of catatonic schizophrenia to such a degree that they had to be restrained. The observers were also aware of the fact that only active drugs were given as they were aware of the date of alternation from one drug to another. But only the dispensary in Copenhagen knew the code according to which the patients were assigned to chlorpromazine or thioridazine by random numbers. The tablets were identical with respect to taste and appearance. The code was not revealed until we had assessed the result of the treatment in each case.

The patients lived in different wards and remained in the same ward throughout the study.

Besides the usual checking of the patients carried out on ward rounds by the nursing staff and by doctors, the state of the patients was evaluated three times during the preliminary period and once every fortnight thereafter. This was done partly by clinical description and partly by marking 0, +, ++, +++ on special sheets referring to washing, dressing, eating, occupation, and to interpersonal contact, sociability, hallucinations, delusions, and motor activity. E.g. 0 on dressing meant that the patient was completely unable to dress himself, while +++ meant that he could do so without any help; correspondingly 0 on interpersonal contact meant that the patient appeared completely autistic and +++ that the interpersonal contact was felt within normal ranges, etc. On the same sheet under 8 headings, the degrees of side-effects clinically visible were noted. Finally a number of laboratory tests were made at the same intervals.

All the ratings were done by the three authors each taking care of the patients in his special wards. The final evaluation of improvement was made on account of these simplified rating scales, the notes in the records, the authors' personal clinical impression of the patients, and the observations made by the nurses. In this connection it can be mentioned that the wards each count 20—30 patients and that the number of nurses for each of these wards during day-time generally is two-three registered nurses and one student nurse. We consider an evaluation procedure as the mentioned as more valuable than solely judging from elaborate, often pseudo-exact rating scales. By the use of rating scales much significant information may drop out while an

abundance of irrelevant symptoms often are registrated and many an error may sneak in despite all caution.

**Dosage.** As well chlorpromazine as thioridazine were given as hydrochloride in coated tablets.

In preliminary tests, chlorpromazine and thioridazine were found to have approximately equal potency, thioridazine and chlorpromazine were started in doses of 25—50 mg three times daily increasing by 25—50 mg per dose (75—100 mg daily) every 5th day until a suitable clinical effect was forthcoming, or side-effects made further increase dangerous or even necessitated reduction of the dose. In this manner we tried to determine the optimum therapeutic dose for each patient. The maximum dosages are tabulated in Table 2.

Table 2. *The distribution of the maximum dosage in mg/24 hours for all patients who went through the study*

| Max. dose in mg/24 hours | | <100 | 100 to 175 | 200 to 275 | 300 to 375 | 400 to 475 | 500 to 575 | 600 to 675 | 700 to 775 | 900 | Total number of patients |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of patients while on Chlorpromazine | M | — | — | 1 | 12 | 12 | — | 2 | 0 | 0 | 27 |
| | F | 1 | 1 | 3 | 11 | 3 | 1 | 3 | 2 | 0 | 25 |
| Number of patients while on Thioridazine | M | — | 1 | 3 | 12 | 9 | — | 0 | 1 | 1 | 27 |
| | F | — | 2 | 2 | 12 | 4 | 1 | 3 | 1 | 0 | 25 |

The change-over from one preparation to another was made on a definite date without altering the prescribed dose.

This procedure was considered more likely to yield reliable comparison than a dose fixed in advance, in which case attaining the optimum therapeutic dose in each patient would be a matter of chance.

At weekly intervals during the investigation Dr. H. K. Neve (1958 and 1961) ascertained by the use of a special chemical method whether the patients excreted the medicine or its catabolic products. This revealed that 4 male patients under chlorpromazine did not take the prescribed dosage. The tablets then were crushed or given in solution.

## Results

Table 3. *Summarized treatment results*

| | |
|---|---|
| Patients starting | 61 |
| Patients dropped out | 9 |
| Patients completing the study | 52 |
| Improved | 39 |
| Unchanged | 11 |
| Worse | 2 |
| Similar reaction to thioridazine and chlorpromazine | 27 |
| Better under thioridazine | 13 |
| Better under chlorpromazine | 12 |

*Assessment of the effects*

The investigation was completed in 52 out of 61 cases.

In 27 patients the mental state was unchanged during the two periods of investigation, while 8 patients were judged as better in period I and 17 patients in period II.

On disclosure of the code it was found that of the 25 patients who had reacted differently to the two drugs, 13 were judged to have improved under thioridazine and 12 under chlorpromazine. In the remaining 27 cases, the clinical effect was found equal after both drugs.

It is evident that no refined statistical procedures are needed to ascertain the fact that from this comparative study of thioridazine and chlorpromazine in chronic schizophrenia no conclusion can be drawn stating the superiority of either of the drugs. This was one of our primary problems in this study.

Even if the primary purpose of the present investigation was to compare the advantages and disadvantages of the two preparations, we should like to illustrate the efficiency of both by just mentioning the fact that, of the 52 patients who completed the investigation, 32 grew worse during the preliminary period without medicine, and improved later on. On the 20 whose condition was unchanged during the preliminary period, 7 improved later on under medication, while 11 remained unchanged from the beginning to the end of the three periods, and only two patients got worse during a single investigation period.

One might be tempted to consider the preliminary period as a real "no treatment period" and compare the states during this period with the thioridazine and chlorpromazine periods (despite the fact that one has to reckon with the placebo-factor during the treatment periods). The preliminary period, however, was not procured for as a period without drugs as such. It was established with the sole aim of making the effect of previous drug therapy disappear, so that the first period might be safely compared with the last 12 of the 16 weeks of treatment in period II; the first 4 weeks of the second period being excluded for the same reason, "to avoid overlapping".

Regarding the validity of the rating the reader is referred to the above-mentioned statements according to which the authors consider clinical judgement of experienced psychiatrists and psychiatric nurses more valuable than rating scales alone. In the present study the clinical "double-blind" statements must be considered unbiased as to the effects of the two drugs investigated. In a few instances one of the authors had to fill out the sheets for some patients in the wards of one of the other authors. A certain judgement of the reliability could thus be performed. The degree of agreement was found satisfactory.

Table 4. *Complications etc. in the nine patients who dropped out of the study. All patients suffered from schizophrenia of 14—30 years' duration*

| Initials | Sex | Age | Maximum dose of thioridazine/ 24 hours | Complications etc. under thioridazine | Maximum dose of chlorpromazine/24 hours | Complications etc. under chlorpromazine | Reason for exclusion of series |
|---|---|---|---|---|---|---|---|
| D.P. | F | 59 | 300 | (Leucocytes dropped to 2800 and 2800) | 300 | Leucocytes dropped to 2720 and finally to 2200 | Myelotoxic effect of chlorpromazine |
| V.V. | M | 52 | 225 | Leucocyte count 1800 | 0 | | Myelotoxic effect of thioridazine |
| G.Å. | F | 45 | 25 | One hour after first dose malaise, paleness and cyanosis. One hour and a half after second dose (on the succeeding day) transient tachycardia (pulse 168—140) | 0 | | Suspected allergic reaction to thioridazine |
| K.J. | F | 55 | 750 | Increasing disorderly behaviour | 375 | No side-effects (fair therapeutic effect) | Lack of clinical effect of thioridazine |
| J.P. | F | 74 | 150 | Suddenly dropped dead on third day of medication. Autopsy revealed extensive arteriosclerosis and occlusion of the right coronary artery | 0 | | Death probably not due to thioridazine |

| | | | | | | |
|---|---|---|---|---|---|---|
| O.J. | F | 55 | 375 | No side-effects | | |
| V.M.N. | F | 62 | 0 | | 375 | Vomiting and subileus five weeks after starting on chlorpromazine |
| | | | | | 300 | Developed ileus on 11th day of medication. X-ray revealed colon elongatum. Has previously and later tolerated chlorpromazine |
| A.M.N. | F | 53 | 225 | | 0 | |
| M.M.B. | F | 54 | 0 | | 150 | |

Subileus. Chlorpromazine considered likely contributory cause

Ileus. Doubtful whether chlorpromazine can be considered contributory cause

Medication stopped due to attack of nephrolithiasis resulting in operation. This cause considered irrelevant

Patient got very excited when blood samples were taken

*The cases in which the investigation had to be broken off*

In 9 patients (1 male, 8 females) it was not possible to complete the investigation. These cases have been tabulated in Table 4.

We do not consider the results above any general justification for preferring either of the preparations.

*Clinical side-effects in the patients who completed the therapeutical investigation*

Every fortnight the presence or absence of the 8 side-effects shown in Table 5 were registered on a schedule.

Other side-effects observed comprised: 1 patient treated with chlorpromazine developed edema of the face, 2 developed transient tachycardia. One patient under chlorpromazine and one under thioridazine complained of vertigo. One attack of convulsions was observed in a patient having thioridazine, electroencephalography showed aberrations of a focal type.

If the risk of developing rigidity was the same under thioridazine treatment as under chlorpromazine treatment the probability to find a distribution as shown in Table 5—where only 7 patients reacted with one of the drugs—is $\frac{1}{2^7}(21+7+1) = 23\%$. This means that from the table we cannot infer that

rigidity is a less common side-effect under thioridazine than under chlorpromazine treatment.

For tremor on the other hand the probability—determined in the same way—is only 3%.

Table 5. *Side-effects in the 52 patients who completed the investigation*

| Symptom | On chlorpromazine only | On thioridazine only | On both chlorpromazine and thioridazine | Total number of patients with side-effects |
|---|---|---|---|---|
| Fatigue | 3 | 3 | 8 | 14 |
| Torpor | 7 | 6 | 4 | 17 |
| Rigidity | 5 | 2 | 5 | 12 |
| Tremor | 5 | — | — | 5 |
| Oculogyric crises | — | — | — | 0 |
| Salivation | — | — | 2 | 2 |
| Skin rash | 5 | 1 | — | 6 |
| Dyspepsia | 4 | 3 | — | 7 |

With respect to skin rash the probability is found to be 11%, i.e. the difference is not significant statistically.

Nor do the results of this examination imply that either preparation is definitely to be preferred, but thioridazine seems less liable to cause tremor.

*Laboratory tests of the patients who completed the therapeutical investigation*

The results appear in Table 6.

Table 6. *Number of abnormal findings in laboratory tests in the 52 patients who completed the therapeutic investigation. Number of patients with abnormal laboratory findings*

| Test | On chlorpromazine only | On thioridazine only | On both chlorpromazine and thioridazine (not given simultaneously) | Total number of patients with abnormal laboratory findings |
|---|---|---|---|---|
| Leucocyte count less than 3000 | 2 | 2 | — | 4 |
| Leucocyte count between 3000 and 4000 | 8 | 7 | 13 | 28 |
| GPT above 35 units | 2 | 3 | 1 | 6 |
| Alkaline phosphatases above 10 units | 1 | — | — | 1 |
| Systolic arterial pressure less than 100 (auscultation) or less than 90 (palpation) | 5 | 7 | 2 | 14 |

The drop in the *leucocyte count* was in all cases of short duration. *Glutamic acid—pyruvic acid—transaminase* (GPT) was determined by WROBLEWSKI's test. *Alkaline phosphatases* were found slightly above 10 units (KING and ARMSTRONG's test) temporarily in one patient

taking 225 mg chlorpromazine per day, but the value returned to normal in spite of continued treatment with increasing doses. *Decline in blood pressure* below 100 mm (auscultatory) appeared in 9 males, 2 taking chlorpromazine, 6 thioridazine and 1 when taking either preparation. Decline in blood pressure below 90 mm (palpatory) appeared in 5 females, 3 taking chlorpromazine, 1 taking thioridazine, and 1 taking either. Nor does this examination point to any definite difference in the value of the two drugs.

*Other clinical investigations*

The preliminary paper already mentioned refers to clinical information from Switzerland and the USA stating in much the same words that thioridazine has a sedative and antipsychotic effect practically corresponding to that of chlorpromazine, but has fewer or less troublesome side-effects.

In a later publication from Norway concerning a double-blind test in which thioridazine and placebo respectively were given to 44 female patients for 4 weeks' periods HAUG states that the results after thioridazine were significantly better than those after placebo. All these patients had previously been treated with chlorpromazine and, as regards the number of patients improved, the effects of both drugs were equal, 19 patients obtaining the same advantage from the two preparations, 13 having a better reaction to thioridazine and 12 to chlorpromazine. As regards quality, there were certain differences, especially as thioridazine seemed to have less hypnotic effect than chlorpromazine and possibly some stimulating effect as well. On the other hand chlorpromazine seemed to act more quickly and possibly had a more powerful antipsychotic effect.

DELAY et al. state that chlorpromazine is to be preferred to thioridazine in pronounced cases of agitation, but that the clinical effect of the two drugs is otherwise almost equal. Thioridazine was perhaps less efficient in the treatment of chronic psychosis, but the difference was not pronounced, and since thioridazine was less soporific and caused fewer complaints, patients were comfortable while receiving it. It was mentioned that galactorrhea was a more common complication with thioridazine than with other phenothiazines or reserpine. In 2 of 35 patients the authors observed conspicuous extra-pyramidal symptoms, but not until 300—500 mg daily had been administered for 3 months.

Other clinical reports stress the absence (HAUG) or great rarity of extra-pyramidal symptoms in connection with thioridazine treatment (SAUTER: 2 cases out of 79 treated, BRUNOLD: 1 out of 89). Allergic exanthemas and photosensitivity practically never appeared, and serious

toxic side-effects such as agranulocytosis or icterus have not been reported. On the other hand MAY, SELYMES, WEEKLEY and POTTS (1960) have registered reduced power of sight, deposition of pigments and edema of the retina in patients who took very large doses of thioridazine, if the total amount given exceeded 85 g over an average period of 43 days.

## Conclusion

It is concluded that thioridazine and chlorpromazine have about similar efficiency in treatment of chronic schizophrenia. The frequency of complications and side-effects was not essentially different for the two drugs.

Tremor seemed to be less frequent under thioridazine, although the material does not allow definite conclusions on this point.

As a small number of patients who did not respond to other treatment improved under thioridazine, this drug may have a place in the antipsychotic drug armamentarium in addition to chlorpromazine.

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## Summary

After a preliminary period of 3 weeks without medicine, 61 chronic schizophrenics were treated with either thioridazine or chlorpromazine for 12 weeks and then vice versa for 16 weeks, using a double-blind technique.

9 patients had to be withdrawn from the investigation because of complications. Tremor seemed to be a less frequent side-effect under thioridazine treatment. Otherwise no differences with respect to the frequency of side-effects or complications could be established.

The clinical effect of the two drugs was found equal in 27 patients. 13 patients improved more under thioridazine and 12 under chlorpromazine.

Thioridazine and chlorpromazine are of similar efficiency in treatment of most cases of chronic schizophrenia. Some patients, however, respond better to one drug and some respond better to the other.

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***Short Communications · Kurze Originalmitteilungen***
***Communications brèves***

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# The Selective Action of Chlorpromazine on Behavior Suppressed by Punishment*

By

JAMES A. DINSMOOR and DAVID O. LYON

With 1 Figure in the Text

*(Received April 14, 1961)*

One of the most popular of the clinically derived interpretations of human behavior disorder is in terms of the complications that may arise when a given sequence of behavior leads at the same time to desirable consequences, which serve to reinforce it, and undesirable consequences, which tend to suppress it. Theorists of a psychoanalytic persuasion, for example, have represented this as a conflict between the pleasure-seeking "id" and the repressive "superego". Such a pattern, therefore, would seem to be an important setting in which to examine the action of various drugs reputed to be useful in treating behavioral disorders.

In current behavioral theory, performance in this situation is viewed as the resultant of a direct mechanical competition between the positively reinforced behavioral sequence and opposing reactions maintained by their effectiveness in delaying or avoiding the punishment (DINSMOOR 1954, 1955; MOWRER, SKINNER). It is important, therefore, not only to determine whether the effects of a given agent are general or specific but also to determine whether they are mediated by the original, positively reinforced behavior or by the opposing avoidance behavior. The obvious solution is to test both punished and nonpunished behavior more or less concurrently, maintaining the same schedule of positive reinforcement in both cases.

This may be accomplished by alternating the two conditions successively throughout the experimental session, using a distinctive stimulus to indicate which contingency is in effect at a given time (DINSMOOR 1952). The selective effect of the drug may then be determined by comparing the simultaneously punished and rewarded per-

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formance with that obtained under reward alone conditions. Note that this technique differs from conventional measures of drug action on avoidance behavior (HERZ) in that it calls for an increment where conventional measures call for a decrement in performance. For our first test of the effectiveness of this technique we have chosen one of the best known of the behaviorally active compounds, chlorpromazine hydrochloride, and have plotted an individual dose-response curve for each subject.

## Method

The subjects were five male albino rats, about four months old at the beginning of training. They were provided with daily feedings of Wayne Lab Blox for Rats and Mice sufficient to maintain body weights at approximately 80% of their *ad lib.* level.

The testing chamber measured $5^5/_8$ by 10 in. on the inside, $6^3/_4$ in. high. The walls were aluminum, the ceiling transparent plastic, and the floor composed of sections of brass tubing forming a shock grid (DINSMOOR 1958). This unit was enclosed in a light proof and sound deadened shell ventilated by a 15 c.f.m. blower.

At one end of the test chamber, a response lever (VERHAVE) was mounted $3^1/_2$ in. above the grid. This was adjusted to operate at 10 gm. pressure, with an excursion of less than 1 mm. Noyes food pellets weighing 97 mg. were delivered to a tray accessible to the animal through a 2 by $1^1/_2$ in. opening directly below the bar. Auditory signals were provided by a 4 in. speaker connected through an impedance matching transformer with a Grason-Stadler 455B white noise generator (equal energy spectrum to 10 000 cycles), set at full gain. The shock grid and the walls and bar were connected through a high speed electronic polarity alternator and a 1 megohm series resistance to an AC shock source set at 870 volts.

The behavioral technique was based on earlier work by DINSMOOR (1952), but is related to techniques currently being used by BARRY et al., by GELLER and SEIFTER, and by GROSSMAN. The animals' behavior was stabilized on a schedule providing food pellets for lever pressing at irregular intervals averaging 4 minutes (VI-4). White noise was then added for alternate two-minute time segments, during which all responses were punished by the administration of a 30 ms. electric shock. Once a discriminative performance had stabilized, preliminary injections of chlorpromazine were initiated.

To determine the effects of various levels of the drug, we tested the animals on the first, third, and fifth days of a weekly cycle. A drug dose was injected on the first day, nothing on the third, and saline on the fifth. The saline control consisted of 9 mg. sodium chloride per cc. distilled water, the drug doses of $^1/_2$, 1, 2, or 4 mg. chlorpromazine

hydrochloride per cc. administered in haphazard order. The injection volume was 1 cc./kg. body weight, subcutaneous. Injections were administered immediately prior to the six hour test session except for one animal, to whom they were given four hours earlier. This animal's record did not appear to deviate from those of other animals.

The same general procedure was also followed in a subsequent replication of the design with a lower level of shock, 2 megohms. The purpose of this replication was to determine whether less severe suppression of the food-reinforced performance would provide a more sensitive testing situation.

## Results

Under severe punishment, the rate (frequency) of responding in the presence of the white noise ranged in individual animals from 0.16 to

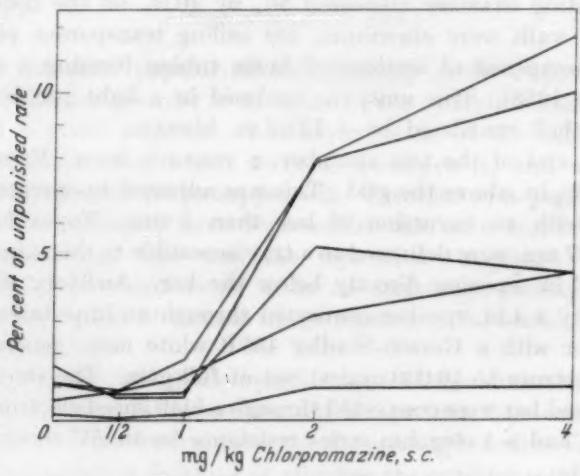


Fig. 1. Curves showing the action of four doses of chlorpromazine on the punished rate of pressing as a percentage of the unpunished rate for individual rats

1.63% of the control rate in the absence of the noise. As may be seen in Fig. 1, this percentage rose fairly consistently with dose level for each animal, and was 4 to 9 times as high at 4 mg. as it was with the saline. It should be noted, however, that these figures are based on relative rates. The trend for absolute rate of responding in the presence of the noise is not so clear, and the major change in absolute performance was a decline in the control rate. Thus, the selective effect of the chlorpromazine in maintaining the punished behavior is accompanied by a general decline in activity.

Data obtained with the milder punishment were less sensitive, showing only a trend related to the order in which the doses were administered to each animal.

## Discussion

There are three simple generalizations with which these findings would in themselves be consistent. First, since there is no clear demonstration of an absolute increase in the punished rate, the relative increase might be interpreted as an artifact resulting inevitably from any decrease in general activity. No such relative increase is obtained, however, when the level of activity is reduced by providing the animal with more food between experimental sessions (DINSMOOR 1952). Therefore, this interpretation cannot be supported.

Second, the relative increase in punished rate could be attributed to a deterioration in the discriminative powers of the subject. When the animal is unable to distinguish the two conditions as clearly as before, the two rates might tend to converge. However, no evidence for the impairment of simple auditory discriminations has appeared in earlier studies of the behavioral effects of chlorpromazine (e.g., WEISSMAN).

Finally, the present data might be interpreted as indicating that chlorpromazine has a selective effect on the punished behavior, accompanied by a more general sedative or depressive effect. This selective effect could be exercised through a reduction in the animal's sensitivity to shock, since previous data (DINSMOOR 1952) indicate that severity of shock is one of the factors governing the ratio of the punished to the unpunished rate of performance in this situation. However, this interpretation is to some extent discounted by the data (see HERZ) showing that animals continue to perform responses necessary to escape from shock after it has come on even at doses under which they will no longer perform responses that prevent the onset of the shock in the first place. An interpretation in terms of a selective effect of the drug on the avoidance mechanism itself would seem to be the preferred conclusion and would seem consistent with clinical accounts of the action of this compound.

## Summary

Rats were trained to press a response lever to obtain pellets of food at irregular intervals averaging four minutes. A white noise signal was added during alternate two minute segments of time, during which a schedule of punishment for all responses was superimposed on the food reinforced behavior. The punishment was sufficiently severe to reduce the rate (frequency) of pressing to about 1 per cent of its nonpunished level. Five individual dose-response curves were then plotted to show the effects of $^1/_2$, 1, 2, and 4 mg./kg. chlorpromazine, s. c., on the punished rate as a percentage of its nonpunished counterpart. Fourfold to ninefold increases were registered for individual animals. This result was interpreted in terms of a selective action of the drug on the punished behavior, combined with a more general sedative or depressive effect on the food reinforced behavior.

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# Tryptamin-Katatonie, eine cholinergische Hypofunktion im zentralen Nervensystem

Von

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Frühere Versuchsergebnisse (Ernst et al. 1961) haben zum Schluß geführt, daß das Auftreten einer Katatonie nach Tryptamin-Verabreichung die Folge einer Verdrängung des 5-Hydroxytryptamins (5-H.T.) von gewissen Receptoren im ZNS ist, daß Tryptamin eine geringere „Eigen-Aktivität" (intrinsic activity) hat als 5-H.T. und daß das Entstehen der Katatonie einer 5-H.T.-Hypofunktion entspricht.

Bei der Durchführung dieser Versuche fiel uns auf, daß die Phänomene, die bei der Katze nach Injektion von 5-H.T. auftreten, typisch parasympathischer Natur sind und vollkommen übereinstimmen mit den Phänomenen, welche beim Versuchstier beobachtet werden, wenn der Abbau des Acetylcholins durch eine subcutane Eserin-Injektion gehemmt ist, nämlich: Speichelfluß, Miosis, Defäkation, Erbrechen, rasche Atmung und, nach höheren Dosen, Tremor der Kopf- und Extremitätenmuskeln, epileptoide Krämpfe, abwechselnd mit Muskelschwäche. Faßt man diese Beobachtungen zusammen. so kommt man zur Auffassung, daß dem Katatonie-Syndrom nach Tryptamin-Verabreichung im wesentlichen ein parasympathicolytischer Effekt zugrunde liegt und möglicherweise durch Erhöhung des Acetylcholingehaltes des ZNS mittels einer Eserin-Injektion aufgehoben werden kann. Diese Hypothese haben wir experimentell geprüft.

Mit dieser Hypothese stehen die Resultate von Feldberg und Sherwood (1954a/b) in scheinbarem Widerspruch. Durch eine Dauer-Kanüle im lateralen Gehirnventrikel der Katze injizierten diese Autoren diverse Substanzen, unter anderem Acetylcholin, Eserin und Atropin. Nach Verabreichung von 10—20 $\mu$g Acetylcholin setzten die Katzen sich oder legten sich hin, leckten und kratzten sich, die Augen waren halb geschlossen; später entwickelte sich ein Syndrom, das einer akinetischen Epilepsie ähnelte. Nach Verabreichung von Dosen bis zu 1 mg zeigten die Tiere starke Konvulsionen, später Stupor und Katatonie; auf starke Reize reagierten die Tiere immer mit Laufen und Springen ohne Lähmungssymptome.

Nach Eserin-Injektion beobachteten die Autoren drei Stadien, die einander überlappten:

1. Stadium nach einer Dosis von 10 $\mu$g: Die Tiere speichelten, leckten, wuschen und kratzten sich, waren aktiv und liefen rasch umher (usually active, moving about swiftly).

2. Stadium nach Dosen von 20—100 $\mu$g: Die Tiere saßen oder lagen, gingen nicht spontan. Nach Reizung reagierten die Tiere mit schnellen plötzlichen kriechenden Bewegungen. Dann und wann trat Erbrechen und Defäkation auf. Nach 30—40 min waren die Tiere wieder ganz normal.

3. Stadium nach noch höheren Dosen: Die Tiere wurden stuporös und kataton, nicht hypoton.

Nach Injektion von 150 $\mu$g Atropin wurden die Katzen lebhafter und unruhig. Nach 200—300 $\mu$g Atropin zeigten sie Speicheln, Defäkation, Erbrechen, Tachypnoea und völlige Erschlaffung. Eine Katze, nach 10 $\mu$g Acetylcholin stuporös geworden, wurde nach Injektion von 50 $\mu$g Atropin viel lebhafter.

## Methodik

Unsere Versuche wurden mit lebhaften, aber gut hantierbaren Katzen von 2—2$^1/_2$ kg Gewicht durchgeführt. Es wurden verwendet: Tryptaminhydrochlorid Hoffmann-La Roche, Eserinsalicylat und Atropinsulfat vom Großhandel.

Die Beschreibung der Kriterien, welche in den vorliegenden Untersuchungen angewandt wurden für die Bestimmung von An- bzw. Abwesenheit von Katatonie, Hypokinese, Negativismus, Katalepsie, Stupor und normaler Motorik, ist in der früheren Mitteilung (Ernst et al.) ausgeführt.

Verabreicht wurde Tryptamin intraperitoneal in wäßriger Lösung 20 mg/ml; sub-occipital 2 mg/0,1 ml in 0,9%igem NaCl gelöst nach der Methode von Méhes; Eserinsalicylat subcutan in 0,9% NaCl in der Konzentration von 0,5 mg/ml; Atropinsulfat subcutan 10 mg/ml in Aq. dest.; Iproniazid (Marsilid) Hoffmann-La Roche, subcutan, 50 mg/ml in Aq. dest.

## Ergebnisse

In drei Versuchen spritzten wir je drei Katzen (total neun Tiere) mit 50 mg/kg Tryptamin intraperitoneal, eine Dosierung, die uns aus früheren Untersuchungen als zweckmäßig bekannt war (Andel). Nach 5—10 min trat Katatonie auf; 5 min später wurde 0,5 mg/kg Eserinsalicylat subcutan injiziert, eine Dosis, welche dieselben Symptome hervorruft, wie sie von Feldberg und Sherwood (1954a/b) als erstes Stadium der Eserinwirkung beschrieben wurde. Etwa 15 min nach der Injektion zeigten die Tiere Pupillenerweiterung, starken Speichelfluß und Defäkation. Stupor und Katalepsie waren verschwunden, nur Hypokinesie

und Negativismus waren noch vorhanden. 30 min nach der Eserin-Injektion waren die katatonen Symptome völlig aufgehoben, während normal nach dieser Tryptamin-Injektion die Katatonie stundenlang bestehen bleibt. Dieselben Versuche wurden noch einmal wiederholt an Tieren nach Vorbehandlung mit Iproniazid. Wie vorhergehende Versuche (Ernst et al. 1961) zeigen, dauert die Tryptamin-Katatonie nach Vorbehandlung mit Iproniazid viel länger. Auf diese Weise konnte kontrolliert werden, ob die Katatonie wieder auftaucht, nachdem die Eserin-Injektion ausgelöscht war. Außerdem kam nun auch der Abbau des Tryptamins bei der Beurteilung der Resultate nicht in Frage.

Drei Versuche, mit je drei Katzen (total neun Tiere) wurden durchgeführt. Die Iproniazid-Vorbehandlung betrug 100 mg/kg subcutan. 16 Std später wurden 20 mg/kg Tryptamin intraperitoneal injiziert. Nach 5 min zeigten die Tiere zwangsmäßige Bewegungen der Extremitäten, die etwa 1 Std erhalten blieben; darauf trat Katatonie ein. Nachdem die Katatonie 10 min deutlich anwesend war, erhielten alle Tiere 0,5 mg/kg Eserinsalicylat subcutan verabreicht; 10—15 min später traten Salivation und Pupillenerweiterung(!) auf; Stupor und Katalepsie waren nicht mehr vorhanden; Hypokinesie und Negativismus anwesend; $^1/_2$ Std später waren auch diese katatonen Symptome ganz verschwunden und die Motorik während $1^1/_2$ Std vollkommen normal.

Sodann kehrte die Katatonie zurück und dauerte noch einige Stunden an, da offenbar inzwischen die Eserin-Injektion abgeklungen war und der Tryptamin-Effekt wieder in den Vordergrund trat. Zur Prüfung dieser Resultate, an anderer Tierart, wurden zwei Kaninchen in gleicher Weise behandelt. Es zeigte sich ein vollkommen identischer Verlauf der Symptome wie bei den Katzenversuchen.

Umgekehrt wurde auch geprüft, wieweit Eserin imstande ist, das Entstehen der Katatonie durch Tryptamin zu verhindern. Dafür dienten weitere drei Versuche, wobei jedesmal drei Katzen subcutan 0,5 mg/kg Eserin verabreicht wurde. $^1/_2$ Std nach der Eserin-Injektion erhielten sie 2 mg Tryptamin (pro Tier) in die Cisterna magna. Diese Dosis Tryptamin verursacht gemäß früheren Untersuchungen (Andel, Ernst et al.) bei nicht vorbehandelten Katzen regelmäßig Katatonie. 10 min nach der Eserin-Injektion zeigte sich Speichelfluß, Tachypnoea und Durchfall; 5 min später leichter Tremor an den Vorderpfoten und geringe Erregung. Nach der Tryptamin-Injektion trat an keinem dieser Tiere Katatonie auf, hingegen verschwanden der Tremor und die Erregung.

Damit war festgestellt, daß die von Tryptamin verursachte Katatonie durch Eserin-Vorbehandlung verhütet bzw. aufgehoben werden kann.

Ein weiterer experimenteller Beweis sollte bestätigen, ob der Antikatatonie-Effekt des Eserins auf einer Erhöhung der Acetylcholin-

Wirkung im ZNS beruht. Dafür wurde der Anti-Acetylcholin-Effekt von Atropin benützt. Falls unsere Hypothese richtig ist, muß Atropin einen katatonen Zustand erzeugen, oder es müßte nach Verabreichung von Atropin viel weniger Tryptamin wie normal benötigt werden, um ein vollständiges Katatonie-Bild zu erzeugen.

Zu diesem Zwecke wurden drei Versuche mit je 2 Katzen durchgeführt. Zwei Katzen erhielten subcutan 10 mg/kg, 2 Tiere 15 mg/kg und 2 Tiere 20 mg/kg Atropinsulfat. Die Katzen, welche 10 bzw. 15 mg/kg Atropin erhalten hatten, wiesen Hypokinesie und Negativismus auf. Größere Atropin-Dosen machten die Tiere lebhafter und unruhig. Allen Tieren wurden 30 min nach der Atropin-Injektion 20 mg/kg Tryptamin intraperitoneal verabreicht. Diese Dosis erzeugt an normalen Katzen niemals Katatonie. Die unruhigen Tiere (20 mg/kg Atropin) reagierten mit Erregung, aber die beiden anderen Gruppen (10 und 15 mg/kg Atropin) zeigten Hypokinesie und Katalepsie. Dieser Zustand dauerte etwa $^1/_2$ Std, danach trat Erregung und Hyperkinese auf. Die Dosierung des Atropins war offenbar zu hoch.

Deshalb wurde an zwei weiteren Katzen die Atropin-Dosierung erniedrigt und 5 mg/kg subcutan injiziert. Beide Tiere zeigten nun eine deutliche Katalepsie, welche nach einer anschließenden Tryptamin-Injektion, 20 mg/kg intraperitoneal, zur Katatonie führte. Diese dauerte 1—$1^1/_2$ Std, wonach die Tiere sich ohne Erregung erholten.

Diese Atropin/Tryptamin-Katatonie konnte an zwei weiteren Katzen durch eine 5 min später anschließende subcutane Eserin-Salicylat-Injektion (0,5 mg/kg) innerhalb 30 min völlig aufgehoben werden. Aus diesen Versuchen geht also hervor, daß die Möglichkeit besteht, mit Atropin Katalepsie zu erzeugen; diese Katalepsie kann durch eine anschließende Tryptamin-Dosis, welche selber keine Katatonie erzeugt, zur Katatonie verstärkt und letztere wieder durch Eserin aufgehoben werden.

## Diskussion

Die Resultate unserer Versuche ergeben eine eindeutige Bestätigung der von uns in der Einleitung aufgestellten Hypothese. Das Katatoniesyndrom, welches durch Tryptamin-Verabreichung provoziert wird, kann durch Erhöhung des Acetylcholingehaltes des ZNS, mittels einer Eserin-Injektion, aufgehoben werden.

Ebenso zeigte sich, daß Vorbehandlung mit Eserin imstande ist, das Auftreten eines Tryptamin-Katatoniesyndroms zu verhüten. Der Widerspruch unserer Resultate mit Atropin gegenüber denjenigen von Feldberg und Sherwood beruht vielleicht auf einer Dosierungsfrage. Auch wir konnten nach hohen subcutanen Dosen Atropin (20 mg/kg) Erhöhung

der Aktivität und Unruhe an den Katzen beobachten, wie sie FELDBERG und SHERWOOD, nach Dosen von 50—150 $\mu$g intraventrikulär injiziert, beschrieben haben. Verabreichten wir aber kleinere Atropin-Dosen subcutan (5 mg/kg), so zeigten die Tiere Hypokinesie und Katalepsie. Den Effekt von kleineren intraventrikulär injizierten Dosen haben FELDBERG und SHERWOOD leider nicht erwähnt.

Daß Verabreichung von Acetylcholin oder Eserin in den Experimenten von FELDBERG und SHERWOOD an Katzen Katatonie und Stupor zur Folge hatte, während sie in unseren Experimenten diese Symptome gerade verhüteten oder aufhoben, entbehrt zur Zeit einer plausiblen Erklärung. Auch hier liegt möglicherweise eine Dosierungsfrage zugrunde. FELDBERG und SHERWOOD injizierten 10 $\mu$g Eserin intraventrikulär, und die Tiere zeigten Speicheln, sie leckten, wuschen und kratzten sich, waren aktiv und liefen rasch umher. Es sind dies dieselben Symptome, welche auch wir nach subcutaner Eserin-Injektion von 500 $\mu$g/kg an den Katzen beobachten konnten; eine Eserin-Dosierung, welche wir in allen Experimenten verwendet haben. Erst mehr als 10mal höhere Dosierungen (100 $\mu$g und mehr), intraventrikulär injiziert, verursachten Stupor und Katatonie. Dosierung und Applikationsweg sind offenbar sehr wichtige Faktoren für den zu erwartenden Effekt.

Wir haben früher festgestellt (ERNST et al. 1961), daß die Tryptamin-Katatonie infolge Verdrängung des 5-H.T. von gewissen Receptoren im ZNS entsteht und somit eine 5-H.T. Hypofunktion darstellt, welche durch Verabreichung von 5-H.T. wieder aufgehoben werden kann.

Aus den vorliegenden Resultaten schließen wir, daß auch Eserin, durch Hemmung der Cholinesterase-Aktivität bzw. Erhöhung des Acetylcholin-Gehaltes im Gehirn diese Katatonie aufheben kann.

Diese Resultate zusammenfassend, gelangen wir zu folgender neuer Auffassung: Tryptamin verdrängt das 5-H.T. von gewissen Receptoren im ZNS, wodurch ein Mechanismus ausgeschaltet wird, der an sich gewisse Acetylcholinwirkungen im ZNS verstärkt.

**Summary**

Catatonia caused by tryptamine can be prevented respectively abolished by eserine.

Atropine can (in moderate doses) produce catalepsia which can be intensified by tryptamine to catatonia and abolished by eserine.

The combination of these results with formerly published data which showed that tryptamine-catatonia can be antagonized by 5-H.T., leads to the hypothesis that tryptamine competes with 5-H.T. on certain receptors whereby a function is eliminated which tends to strengthen certain acetylcholine activities in the C.N.S.

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**Hinweis zur gegenüberstehenden Arbeit BRODIE et al.**

*** With this article, *Psychopharmacologia* has instituted the publication of an additional type of report, to be included under a new rubric, "Conference Proceedings" in future issues of the journal. Such reports are intended to inform the readers promptly of new experimental or clinical data of unusual importance presented at scientific meetings, prior to publication in detailed form. These articles may be submitted for consideration in the same manner as other types of papers (see Directions to Authors), by the chairman or other responsible officer of the meeting or colloquium in question. The general form of these articles is illustrated by the paper of BRODIE et al., published in the present issue. Attention of contributors is directed to the necessitiy for originality of the methods reported, as well as clarity and brevity of presentation of techniques and results.**

**The Editors**

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***Conference Proceedings · Tagungsberichte · Comptes-rendus****

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Colloquium held at the Psychiatric Clinic, University of Basle, August 29, 1961

# Preliminary Pharmacological and Clinical Results with Desmethylimipramine (DMI) G 35020*, a Metabolite of Imipramine

By

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## Introduction

Since the description of the antidepressant action of imipramine (Tofranil) (Kuhn 1957, Kielholz 1958) and its definition as a new type of psychotropic drug (thymoleptic) (Schmidlin 1958), there has been a number of pharmacological, biochemical and clinical studies on the metabolites of this drug. In 1959 the isolation of several metabolites of imipramine was reported (Herrmann and Pulver 1960, Herrmann et al. 1959), including its monomethyl analogue, desmethylimipramine (DMI), a metabolite derived from imipramine *in vivo* by the removal of one methyl group from the sidechain nitrogen. This metabolite was identified as the previously prepared synthetic reference compound G 35020.

Initial pharmacological and toxicity studies of DMI (G 35020) in animals were conducted that same year (Theobald et al.), and initial clinical

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* G 35020 was synthesized in the Research Laboratories of J. R. Geigy S.A., Basle (Patent applications, Swiss priority, September 4, 1959).

* see page 466.

observations in man were made early in 1960 (GRÜNTHAL 1960). Further clinical studies were relatively slow to develop until a fresh impetus was given by the discovery of BRODIE and coworkers that imipramine counteracts the reserpine-like syndrome caused by the Rauwolfia alkaloids and by a number of synthetic benzquinolizines, without lessening the degree of depression caused by chlorpromazine and barbiturates. These workers then made the important observation that imipramine does not exert anti-reserpine effects *per se* but its action is mediated through the accumulation of the metabolic product DMI. The unique pharmacological properties of DMI are reported briefly below and in more detail elsewhere (BRODIE et al. GILLETTE et al. 1961, SULSER et al.

## Pharmacology

Pharmacological screening in some routine tests revealed the following properties of DMI (G 35020). In the isolated intestine it is half as potent as imipramine in inhibiting the contractions caused by acetylcholine, histamine and serotonin. To counteract adrenaline contraction in the seminal vesicle it is only about one-tenth as active as imipramine. DMI is more active than imipramine in potentiating the effects of norepinephrine. For example, DMI potentiates and prolongs the effects of exogenous norepinephrine in raising blood-pressure and in contracting the nictitating membrane. In addition it potentiates and prolongs the effects of electrical stimulation of the nictitating membrane. The findings with respect to blood-pressure and the nictitating membrane are in accord with the much weaker adrenolytic effect of DMI compared with that of imipramine. Tests on the reciprocal effect of imipramine and DMI indicate that the more marked adrenolytic effect of imipramine may have an antagonistic influence on DMI's potentiation of the neurally and humorrally stimulated nictitating membrane. DMI has only a weak depressant effect on the central nervous system. It inhibits the fighting reactions in fish, but is less potent than imipramine. On apomorphine induced vomiting in dogs, DMI has no influence, and the temperature of normal rats is only slightly reduced. The acute toxicity of DMI is about the same as that of imipramine.

It can be seen from these data that the pharmacological profile of DMI (G35020), studied without reference to other drugs, gives little suggestion of its potent clinical antidepressant properties. In this respect the metabolite DMI is in general little different from imipramine (DOMENJOZ and THEOBALD 1959, SIGG 1959, SCHAEPPI 1960). However, an anti-depressant action of both imipramine and DMI is disclosed in their counteraction of the reserpine-like syndrome. For example, pretreatment of rats with imipramine blocks the characteristic syndrome (profound sedation, muscular rigidity, decreased motor activity, blepharospasm, hunch-

back posture) produced by reserpine-like drugs. Experiments in rabbits and dogs show that it also prevents the reserpine-induced increase in parasympathetic activity, e.g. extreme miosis, salivation and lacrimation. These actions of imipramine, like its clinical action, are delayed in onset. The metabolite DMI accumulates in the brain during a period corresponding to this delay, while imipramine itself is barely detectable (GILLETTE et al. 1961).

The metabolite DMI (G 35020), unlike imipramine, exerts no obvious sedation in rats. It is far more potent and in small doses there is no delay in the reversal of the entire reserpine-like syndrome. In fact the anti-reserpine action of imipramine appears to be mediated almost entirely through DMI, and imipramine actually blocks the action of DMI. The action of DMI is quite specific for it does not prevent the effects of chlorpromazine or barbiturates. In addition it does not block MAO nor prevent reserpine from releasing brain amines. DMI not only blocks the effects of reserpine but in high doses can reverse it to produce a unique pattern of hyperactive behavior which persists as long as 25 to 30 hours. This pattern consists of "compulsive" exploratory behavior characterized by ceaseless, steady circling around the perimeter of the cage. Placed on a high platform the animals almost invariably try to leap down. They are essentially unresponsive to external stimuli, including the presence of other rats. The animals walk, but never run, in one direction in a treadmill for hours on end. Deprived of food and water for 24 hours and then given DMI and reserpine, the animals will not eat or drink. The animals appear to be stimulated by an inner drive to which they respond even when life-threatening situations, such as a fall off a high board, arise.

## Clinical findings

DMI, i.e. G 35020, has so far been subjected to "screening" in three Swiss clinics, imipramine in the first place serving as comparative drug. DMI was administered both by mouth and intramuscularly (coated tablets and ampoules of 25 mg), usually in a dosage of 50—75 mg a day.

In the *Geneva Psychiatric Clinic* so far 11 patients have been treated (8 men and 3 women). These cases were diagnosed as depressive states of various kinds, and the drug was administered for periods of up to two months. Positive results of treatment (remission or great improvement) were obtained in 3 patients, while in 2 others at most a slight improvement was observed. In none of the improved patients was a sudden change in the depressive state observed. Neither the antidepressive efficacy nor the side-effects deviated very widely from those of imipramine. It should be mentioned that in three cases a certain stimulation was discernible, but this was expressed above all in an increase in feelings of anxiety. On the basis of the therapeutic results, though still greatly

limited, it is judged that the behavior of this metabolite is scarcely any different from that of its parent substance, imipramine.

In the *Basle Psychiatric Clinic* 12 women and 5 men were treated, whose depressive states were of quite varying origin. Positive results of treatment (remission or great improvement) were obtained in 8 patients, while in 3 others only slight improvement was achieved. One case could not be assessed since appreciable remission had already been attained in this patient by previous treatment with imipramine, nevertheless the improvement remained stable under DMI (G 35020). Among the 5 failures was a woman patient whose state, which before treatment with DMI was of a more apathetic, depressive nature, was transformed into one of agitation and anxiety. In several patients there was a strikingly rapid onset of effect within the first 48 hours of treatment. In 3 cases in particular the lightening of the depressive mood took place almost precipitately.

In a 66-year-old woman patient who had already had to be treated with insulin and electroconvulsive therapy for endogenous depression with features of involutional reaction in 1956 and 1960, another phase began in April 1961. At first various hypochondriacal somatic symptoms were manifest, such as palpitations, smarting of the eyes, a choking sensation in the throat, neuralgia. By July 1961 a marked depressive state had developed: on admission to our clinic the patient showed pronounced retardation of thought and a severely depressed facial expression with distinct VERAGUTH's folds besides her hypochondriacal symptoms. Treatment, initiated with the antidepressant amitriptyline, brought about no improvement. After administration of DMI (G 35020) spectacular improvement was observed within 24 hours, which persisted for the next two weeks. The doctor treating the patient for her hypochondriacal symptoms described her as "by far the most troublesome in the whole ward". The same doctor described the sudden improvement as follows: "The patient, whom I had never before seen smiling, beamed at me for the first time on my evening visit. True, she still complained somewhat, but her facial expression was completely changed".

In several patients an initially improved state deteriorated again on the change-over from parenteral to oral treatment, an observation already known of imipramine. Strikingly enough, even in cases which were on the whole assessed as negative, there was sometimes an initial improvement of mood — though in some cases only a suggestion of such. A certain activating, stimulating and even impelling effect of DMI (G 35020), similar to that observed with MAO inhibitors, was in a few cases unmistakable. On the other hand an euphoriant or even intoxicating effect, such as occurs with amphetamine, was not observed; of 3 patients not included in the test series, who for a short time were given 50—75 mg of DMI a day, 2 showed no psychic change at all; the third patient complained of a certain fatigue. The side-effects were comparatively intense: several patients complained of hot flushes, outbreaks of perspiration, nausea and vomiting. On the other hand no signs of collapse or disturbances in micturition were observed.

In the *Psychiatric Clinic St. Urban* 17 patients — many of them suffering from depressive or apathetic schizophrenia — were treated with DMI (G 35020) often for several weeks, the dosage varying between 12,5 mg twice a day and 25 mg 3 times a day parenterally or by mouth. Here too the increase in activity, frequently manifest within the first 24 hours, was striking, and sometimes even went as far as to resemble a manic state. Accordingly, in many patients sleep disturbances, particularly difficulty in getting to sleep, were also observed. The sudden lightening of a depressive state and the transition into a phase of excitation with disturbed sleep can be illustrated especially clearly in the following case-history:

41-year-old patient in whom an acute paranoid state developed in 1959 which subsided under a course of insulin shock therapy. Recently admitted to hospital owing to delusions of poisoning associated with a depressive mood and psychomotor inhibition. Immediately before admission he had suffered a raptus for which first of all chlorprothixene was administered i.m. Owing to the predominant depressive component therapy was changed to 25 mg of DMI 3 times a day. On the 2nd day of treatment the patient declared that his depression had vanished and he gave the impression of being relaxed. He could laugh. But he complained that he had difficulty in getting to sleep and frequently woke up. The same day, however, he also expressed paranoid ideas again for the first time since they had subsided under treatment with chlorprothixene. The next morning he no longer expressed these ideas but gave the impression of being under great tension and complained again of not having slept.

On the 4th day of treatment therapy was changed to 12.5 mg of DMI twice a day and in the evening 30 mg of chlorprothixene. Owing to further increasing excitation and expression of paranoid ideas again, administration of DMI had to be discontinued on the 5th day.

On the basis of the observations made here it is concluded that DMI (G 35020) unlike imipramine predominantly activates the psychomotor system, and secondarily elevates the mood. Scarcely any side-effects were observed, the tolerability of the drug was good. No changes in blood-pressure, pulse rate, temperature or pathological urine findings were manifest. Neither were there any extrapyramidal side-effects or dryness of the mouth.

## Summary of clinical findings

Altogether the three clinics referred to made observations in 45 patients. The patients were suffering from the following depressive states: depressions of endogenous and involutional origin, psychogenic depressions, schizophrenia with depressive features and other depressive states.

Owing to the varying dosage and the disparity in the individual testers' criteria for evaluation, the therapeutic results can be compared only with difficulty. Nevertheless it may be maintained that about half of all depressive states — apparently independent of their

origin — responded to DMI (G 35020). In about 1/3 of the cases a distinct effect could be discerned (remission or much improved).

On the whole the results so far reported are strikingly good, at least in individual cases, although rapid improvement has also been observed with imipramine. If the results of the individual clinics are compared with each other, it can be said that results of the Geneva Clinic indicate that the effect of imipramine and of DMI are practically identical. This study does not compare strictly with the other clinics because the observation covered only 11 patients most of whom were given only oral treatment. Observations made in the Psychiatric Clinic St. Urban show greater differences in the mode of action between the two substances. The results of the Basle Clinic lie somewhere between those of the two other test centres.

## Discussion

It is known from therapy with reserpine that this substance, although by no means regularly, can bring about depressive states. The question whether and how far this effect of the above-mentioned drug resembles spontaneous clinical depression, remains open, in particular in the endogenous form of depression. The possibility of antagonizing individual effects of reserpine with drugs having a demonstrably antidepressant effect, such as imipramine, was already known. The removal of the described reserpine syndrome reported here for the first time goes in the same direction, but over and beyond this it permits the antidepressive potency of new substances to be tested beforehand in the animal experiment. Nevertheless the relationship between this behavior pattern in animals and its reversibility by specific agents, and human problems of behavior and drug action in mental disturbances is not known. Besides the degree of probable clinical efficacy, the investigation into reserpine antagonism seems also to throw some light on the possible mechanism of action. A comparison of the findings reported here in the animal test (in particular reserpine antagonism) with the clinical effect points in this direction: a more rapid action and greater potency of DMI (in comparison with imipramine) on the reserpine syndrome and in its clinical action against depression in man. Initial results of clinical studies on the same lines in the United States (SULSER et al.), are consistent with the above-mentioned promising clinical findings.

In the evaluation of the preliminary clinical results reported here, it must be taken into consideration that the treatment is of relatively short duration, so that on the basis of the results so far only the "acute" effect of the drug can be evaluated, while the optimal effect during longer therapy cannot yet be estimated. This circumstance is to be taken into consideration in particular when a comparison is made with well known antidepressives such as imipramine.

## Summary

The pharmacological properties of desmethylimipramine (DMI, i.e. G 35020), a metabolic product of imipramine — identified as metabolite III — are described. Substances having a reserpine-like action give rise to a typical syndrome in rats which can be antagonized by DMI in a specific way. However DMI does not affect the sedation produced by chlorpromazine or barbiturates. In addition it does not block monoamine oxidase or affect the release of amines by reserpine. DMI shows greater activity than imipramine and acts with a distinctly shorter latent period. This test arrangement may serve as a model for the study of the potency of antidepressive substances. The provisional clinical results with DMI, synthesized as G 35020, show a close relationship with the described preliminary tests in animals:

1. DMI (G 35020) is an antidepressant which influences various forms of depressive states.

2. The action of DMI (G 35020) in many cases sets in more rapidly than that of imipramine, i.e. within the first 24—48 hours.

3. Frequently DMI (G 35020) has an activating and enlivening effect which seems to be more pronounced than with imipramine, and which — perhaps due to overdosage — may give rise to excessive reactions. However there is as yet no evidence that the drug can cause excitation in the normal subject, a further indication that in reserpine depression as well as in certain clinically observed depressive states a common neural pathway might be disturbed.

Whether DMI (G 35020) is superior to imipramine with respect to its actual antidepressive potency, cannot be judged on the basis of the short experience to date.



## Zusammenfassung

Es werden die pharmakologischen Eigenschaften von Desmethylimipramin (DMI = G 35020), eines Stoffwechselproduktes von Imipramin – identifiziert als Metabolit III — beschrieben. Stoffe mit Reserpinwirkung rufen bei Ratten ein typisches Syndrom hervor, das sich durch DMI in spezifischer Weise antagonistisch beeinflussen läßt. Dagegen wirkt DMI nicht auf die durch Chlorpromazin oder Barbiturate induzierte Sedation. Überdies wird durch dieses Derivat weder die Monoaminooxydase blockiert noch ein Einfluß auf die Depletion von Aminen durch Reserpin ausgeübt. DMI entfaltet eine größere Aktivität und wirkt mit deutlich kürzerer Latenzzeit als Imipramin. Der beschriebene Effekt gegen Reserpin kann als Modell dienen für das Studium der Wirkungsintensität antidepressiver Stoffe. Die vorläufigen klinischen Ergebnisse mit DMI, synthetisiert als G 35020, weisen enge Beziehungen zur beschriebenen Vortestung im Tierversuch auf:

1. DMI (G 35020) ist ein Antidepressivum, das die verschiedensten Arten von Depressionszuständen beeinflussen kann.

2. Der Wirkungseintritt von DMI (G 35020) erfolgt in vielen Fällen rascher als mit Imipramin, d.h. innerhalb der ersten 24—48 Std.

3. Öfter tritt unter DMI (G 35020) eine aktivierende und belebende Wirkung auf, welche ausgeprägter zu sein scheint als bei Imipramin und zu — möglicherweise durch Überdosierung erklärlichen — überschießenden Reaktionen Anlaß geben kann. Soweit aber bis heute bekannt, verursacht der Stoff beim Gesunden keine Exzitation. Dies könnte ein Hinweis sein, daß bei der Reserpindepression und bei gewissen klinischen Depressionen die Leistung gemeinsamer nervöser Funktionssysteme gestört ist.

Ob DMI (G 35020) Imipramin bezüglich seiner eigentlichen antidepressiven Potenz überlegen ist, läßt sich auf Grund der noch zu kurzen Erfahrungen nicht beurteilen.

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